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ORIGINAL ARTICLES.

THE ALLEGED DULLNESS OVER THE APEX OF THE NORMAL RIGHT LUNG.*

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(From the Department of Medicine.)

All textbooks on Physical Diagnosis that I have consulted state that the percussion notes over the apex of the normal right lung are of higher pitch than those over corresponding areas on the left side. Some authors describe the note in the right suprascapular region, especially, as dull, and warn the examiner against mistaking the difference in pitch for evidence of early tuberculosis. Various explanations have been offered for the alleged higher pitch on the right side, such as the position of the eparterial bronchus, the proximity of the right apex to the trachea and the greater development of the shoulder muscles in right-handed persons.

For years I accepted the statements in the textbooks unquestioningly. But when I attempted to demonstrate to students a higher pitch in the right suprascapular region than in the left, the exceptions were so numerous that a reinvestigation of the subject seemed desirable. Second year students† (232 men and 8 women) taking the course on the physical signs of the normal chest, in which they served as subjects for each other, furnished the material for this study. In view of the wide divergence of the results obtained from the prevailing belief that the higher pitch is on the right side, the method of conducting the examinations will be described. In order to avoid variations in technique, I examined personally as many of

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the subjects as possible, roughly some 75%, and all doubtful or disputed cases; and to reduce any error that might arise from the fallibility of the ear in comparing the pitch on the two sides, the "collective" ear of the section was employed; that is, the note was sounded and the student-group (averaging 10) was asked to locate its pitch. In case of disagreement, the percussion was repeated until unanimity was reached or the preponderant opinion was accepted as correct.

Of 223 students, the higher pitch was found on the left side in 158 (70.85%) and on the right side in 65 (29.10%). The pitch was found to be the same on both sides in 8 students and was variable on different occasions in 2 students. The records of 7 students are missing. In 77 students the percussion notes in the right and left supraclavicular and infraclavicular regions were compared with each other and with the note in the suprascapular region. In all but 10 instances, the pitch of the notes in the supraclavicular and the infraclavicular regions corresponded with the pitch in the suprascapular region on the corresponding side.

The results of this study have led me to seek an explanation of the current statement that the pitch of the percussion note over the right apex is higher than that over the left. As stated above, among the reasons usually assigned are the position of the eparterial bronchus and the proximity of the right apex to the trachea. If the eparterial bronchus and trachea have any influence on the percussion note, it is difficult to understand why they would not lower its pitch instead of raising it: if the vibrations reach them, their frequencies should be lessened by the larger air spaces and the pitch of the sound lowered. The tympany found in some cases of pneumonia at certain stages, where the bronchi definitely modify the pitch of the note, lends support to this view. And such an assumption would explain the statistical preponderance of the lower pitch on the right side in this study.

Another reason assigned for the higher pitch on the right side is the greater development of the muscles of the right shoulder in right-handed persons. The thickness and physical state of the structures overlying an area of lung undoubtedly do affect the pitch of the note, for example, over a rib and in an intercostal space. And if care is not taken to damp the vibrations in the thicker muscles of the right suprascapular region, the percussion note will have a higher pitch. But it is easily possible to reduce the vibrations in the muscles to a minimum and obtain the pure pulmonary note. This phase of the subject will be referred to later on.

It may be pointed out that no author reports any statistical studies of the question on normal persons.

Technique of Percussion. Percussion, in my opinion, is the greatest of the arts employed in making a physical examination. Percussion often gives the first clue to the existence of a lesion. It is

capable of disclosing lesions that are difficult to detect by other means, even Roentgen rays, such as localized thickenings of the pleura. To become adept in percussion requires long training. And I am convinced that such training should be conducted by the older and more experienced members of teaching staffs.

So many excellent discussions of the technique of percussion have been written that I hesitate to add another. But since I have made a special study of the subject for many years, it may be that some points in the technique I have come to rely on may be suggestive to others. The discussion will be discursive rather than systematic. The fingers are the only instruments the physician needs for percussion and are the best. Artificial plexors and pleximeters introduce adventitious sounds and make interpretation more difficult. In addition, they completely deprive the examiner of the information he may obtain through the vibration sense—the "feel" of the area percussed. The index finger of the left hand should be used as the pleximeter as it is under easier control than the middle finger. The use of crossed fingers as a pleximeter or the so-called orthopercussion (the pleximeter flexed to a right angle at the 2d phalanx) unnecessarily complicates the procedure and lessens the acuity of perception. The pleximeter should be applied with pressure. The amount of pressure required varies greatly in different persons and in different regions of the same chest. When the chest-wall is thin, the pleximeter need only be placed firmly on the surface; when the chest-wall is thick, and over the scapulæ, much pressure is required, so much in fact that the finger may feel sore after a prolonged demonstration. The object of the pressure is to damp the vibrations in the overlying structures so that the pulmonary note may be obtained in its purest form. It is always advisable to vary the pressure until the observer is satisfied that he is obtaining the note characteristic for the region or for a pathologic lesion. The overlying muscles should be relaxed, especially when delicate shades of pitch have to be evaluated. For example, when comparing the supraclavicular regions, the patient should look straight ahead. If the face is turned to one side, the stretching of the platysma on the opposite side will raise the pitch of the note just as hunching a shoulder raises the pitch of the percussion note over the suprascapular region.

The middle finger of the right hand should be used as the plexor—it is on the central axis of the forearm and hand. The use of two or more fingers is never necessary even in the heaviest percussion and is likely to alter the pitch and distort quality of the sound. The blow should be delivered on the middle phalanx of the pleximeter with the pulp of the finger used as the plexor—striking on the nail or first joint introduces confusion vibrations. The power for the blow is derived from flexing the finger, on the knuckle as a fulcrum, and from the wrist. In the lightest percussion all necessary power

may be derived from the finger alone. Preliminary extension of the wrist facilitates the execution of the movement and preserves the arc through which the end of the plexor must travel in order to lessen the chance of injuring the pleximeter with the nail of the plexor—an important consideration in prolonged percussion. When additional power is desired, the wrist may be sharply flexed. Another method is to fix the wrist and to obtain what additional power is required from the forearm. This method is not recommended until percussing from the knuckle and wrist has become a settled habit.

As the stroke is delivered by the middle finger, the other fingers automatically extend in a compensatory movement. In view of the frequency with which it has been stated that the plexor must be lifted quickly from the pleximeter after striking the blow to prevent damping of the vibrations, for years I have experimented on the subject. Neither I nor the participants in the experiments have been able to detect any variation in the sound or the "feel" of the area when the plexor was allowed to remain lightly on the pleximeter. And I have found that the mental and physical effort required to lift the plexor quickly interfered with concentration on the sound elicited.

The strength of the stroke of the plexor must be adjusted to the local necessities. The rule should be to use the least force possible. The object is to obtain the note of the lung with the least interference from vibrations in the overlying or nearby structures. When the stroke is too hard reverberations alter the quality of the sound. It is rarely possible to obtain the optimum note with the first stroke of the plexor. The force of the blow must be adjusted not only to the thickness of the overlying structures but to the degree of pressure by the pleximeter—there is always an optimum for each of them—to obtain the purest note. This requires an attentive ear and knowledge of many chests both in health and disease.

Palpatory Percussion. The term palpatory percussion has been given several interpretations. I shall use it to mean palpation of the vibrations set in motion by percussion. The percussion may be mediate or immediate. Both procedures are based on the ability of the examiner to perceive vibrations through his fingers and both are susceptible of a high degree of cultivation. My personal preference is for mediate percussion where both pleximeter and plexor participate in the sensations.

The technique of palpatory percussion is similar to that described for audible percussion. The same fingers are used as plexor and pleximeter. The pleximeter is applied with a minimum of pressure—some pressure is required to damp the vibrations set up in the finger itself. This can easily be demonstrated on a desk- or table-top, for example. The blow from the plexor must be so light as to produce little or no sound. Sometimes, however, it is desirable to compare the frequencies of the vibrations with both the finger and the ear.

Strong pressure and a heavy blow blunt the vibration sense. In palpatory percussion the frequencies of the vibrations in adjacent regions are compared by the finger instead of by the ear.

In my contacts with other physicians, the use of palpatory percussion has been most frequently observed in the technique of older practitioners. They evidently had come to rely more on the "feel" of the area than on the sound elicited. And their diagnoses usually were correct. Personally, without conscious intent, I have come to use palpatory percussion more and more, especially in outlining the heart, but in most examinations I employ both methods. Palpatory percussion is likewise useful in locating the lower edge of the liver and demonstrating enlargement of the spleen, when it is difficult to palpate.

In my opinion, the value of palpatory percussion has not been sufficiently emphasized in textbooks. I would suggest that students and younger practitioners cultivate the vibration sense. Palpatory percussion of table-tops, doors, window-panes and frames, will reveal how acute the vibration sense is and how useful it may become in physical examination.

Summary. 1. Textbooks on Physical Diagnosis assert that on percussion a higher pitch is obtained over the right suprascapular region than over the left.

2. In this study of the percussion notes over the apices of the lungs of 223 normal second-year medical students, the higher pitch was found over the left apex in 158 (70.85%) and over the right apex in 65 (29.10%) of the students.

3. It is suggested that the preponderance of the lower pitch on the right side is due to the position of the eparterial bronchus and to the proximity of the right apex of the lung to the trachea.

4. The author's techniques of audible and palpatory percussion are described and the suggestion is made that the "feel" or "resistance" of a region is an expression of the vibration sense.

In conclusion I wish to express my appreciation and thanks to Doctors John E. Sawhill, William B. Rawls, Robert P. Wallace, Hannibal DeBellis, Louis L. Shapiro, and Max P. Cowett, formerly my assistants, for their help in obtaining the data on which this communication is based.

THE RÔLE OF THE VIBRATION SENSE IN PERCUSSION.*

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Vibrations are the chief media through which all animals, from ameba to man, receive information concerning their environment and the changes occurring in it. These vibrations vary enormously

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in frequency, from ultra-violet light to the coarse jars, not affecting posture or equilibration, that may be perceived by any part of or the whole body.

According to Jennings,[9] the naked protoplasm of ameba responds to all classes of stimuli to which any animal responds, including light and mechanical jars. But in the process of evolution to higher orders special receptors have been developed by animals to sift out vibrations within more or less definite ranges of frequency. Some insects have sound-producing mechanisms and tympanal organs and are believed to "hear." In the experiments of Wever and Bray,[20] a cricket responded to vibrations of 250 to 11,000 cycles per second and a katydid to vibrations of 800 to 45,000 cycles per second. Cole[1] concluded from his experiments on the common fresh water flea that the first antennæ are receptors for sound waves. Sound waves in air, even when produced by naval guns (Parker[13b]), quickly spend themselves in water, and fishes have been denied the sense of hearing. But the experiments of Parker,[13a] of Manning[11] and others indicate that fish do hear sounds produced in water, in fact, some fish have developed elaborate systems for the detection of such vibrations in which the skin, the lateral-line and the ear participate. Manning found that goldfish responded to vibrations, produced by a submerged telephone receiver, of from 43 to 2752 cycles per second, with the upper limit for the ear undetermined. Vibrations as slow as 6 per second may also be perceived by the lateral-line. There is evidence that in some fishes the swimming-bladder relays sound waves to the Weberian ossicles and the ear (Evans).[4]

The eyes of man respond to vibrations of 400,000 to 800,000 billions per second; the ears of man respond to vibrations of some 30 to 30,000 vibrations per second (Herrick).[8] In addition to the eyes and ears, less elaborate receptors have been evolved, in man at least, for the detection of vibrations of other frequencies which strike or penetrate the skin, such as infrared rays. Yet the fact that individual cells of the skin react to sunlight, as illustrated by the deposition of melanin, leaves no doubt that they have not lost the primordial function of unicellular organisms individually to perceive vibrations. The vibrations referred to above constitute only small fractions of the total range of vibrations. Roughly speaking, they lie at opposite ends of the scale of frequencies. Wood and Loomis[21] found that supersonic waves with frequencies of 300,000 to 500,000 per second, of great intensity, destroy protoplasm. But very little is known about the effects of vibrations of other intermediate frequencies upon animal life.

Surprisingly little study has been devoted to the vibration sense in man as a sense function. In physiologies the subject is dismissed with a few lines or paragraphs. Numerous clinical studies have been undertaken chiefly to determine the effects upon the vibration sense of injuries and diseases of the peripheral and central nervous systems

and the pathways of the sensation to the brain. In some of these studies the observations have been extended to include normal persons. Many facts of physiologic and diagnostic significance have been discovered. The tests were carried out for most part with the aid of tuning-forks of different frequencies: in addition, Tilney[18] used the pallesthesiometer* and blasts from a loud speaker. The tuning forks usually were placed over bones and bony eminences, in some instances over soft parts, and held in position until the fork "ran down." It is obvious that these procedures only partially reproduce the conditions of actual life with respect to the propagation, transmission and reception of the vibrations which the body is able to perceive.

The most complete study of the vibration sense in the literature is by Helen Keller.[10] This study fulfills all the criteria of scientific investigation, an unprejudiced mind, repetition of experiment and adequate controls, and is entitled to scientific rating. Miss Keller surely had no theories to prove, her observations have been repeated daily throughout the greater part of her life, and her controls have been human experience. The fact that the study is purely qualitative in no way detracts from its scientific character—it merely opens up another field of inquiry. A knowledge of the physics of sound may satisfy intellectual curiosity but adds nothing to the usefulness of the vibration sense to the individual—or to the enjoyment of grand opera. As has been pointed out, no other student of the vibration sense has duplicated the conditions of actual life in his experiments. The surface area exposed to the vibrations of a tuning-fork is limited to the size of its foot. In Miss Keller's experiments the surface exposed has varied from the finger-tips to apparently the whole body. The tuning-forks have been standardized for the most part to definite frequencies, though in some experiments a number of forks of different frequencies have been used. Miss Keller's observations have included all frequencies that her vibration sense is capable of receiving.

The vibration sense has played the chief rôle among the senses in orienting Miss Keller to her environment. Her observations bear so directly upon the rôle of the vibration sense in percussion that extensive quotations from her report seem desirable. It may be pointed out here that, contrary to what might have been expected, Tilney found Miss Keller's vibration sense no keener than that of the average normal person. When not handicapped by loss of sight and hearing, the individual finds little use for the vibration sense and usually ignores its messages—and possibilities.

Miss Keller states, "I derive much knowledge of every-day matters from the jars and the jolts which are to be felt everywhere in the house. . . . Footsteps vary tactually according to the age, sex, and the manners of the walker. . . . Often footsteps reveal in

* Rydel and Seiffer suggested the term pallesthesia for the vibration sense.

some measure the character and mood of the walker. . . . When a carpenter works in the house or in the barn near by, I know by the slanting, up and down, toothed vibration and the ringing concussion of blow upon blow, that he is sawing or hammering. . . . By placing my hand on a person's lips and throat, I gain an idea of many specific vibrations and interpret them: a boy's chuckle . . . the moan of pain, a whisper . . . a sob . . . a gasp. . . . I have heard the tiger talk by putting my hand on the bars of his cage. . . . There are tactual vibrations that do not belong to skin-touch. They penetrate the skin, the nerves, the bones, like pain, heat and cold. The beat of a drum smites me through from the chest to the shoulder-blades. . . . I listen with awe to the roll of thunder. . . . Fog-whistles are my vibratory nightmares. . . . Every atom of my body is a vibrascope."

There has been much discussion concerning the nature of the vibration sense and how it is mediated. Rumpf,[15] the first to study it quantitatively, concluded that the sensation is transmitted by the cutaneous nerves, like heat, cold, pressure. Treitel[19] thought it distinct from the sense of touch. Egger[3] suggested the term "la sensibilité osseuse" for the vibration sense because he considered the periosteum, ligaments, and capsules of joints the anatomical basis of the sensation. Symns[17] considered the vibration sense distinct from pain and temperature; that it is a mixed sensation closely allied to deep sensibility. According to von Frey,[5] the vibration sense is a function of the skin, with the bones acting as resonators. Gray[6] agrees that vibrations are best perceived through the medium of bones but that it is not necessarily an osseous sensation. In the opinion of Rydel and Seiffer[16] the vibration sense is a special form of sensation, distinct from touch and pressure, a function of deep sensibility, and that all superposed tissues take part in its perception. Tilney has shown that the skin and soft tissues of the webs between the fingers and folds of loose skin picked up by the thumb and finger are sensitive to vibrations. My observations in percussing solid internal organs, such as the heart, liver, and so on, confirm the view that the vibration sense is independent of the senses of touch and pressure. In delimiting the left border of the heart by palpatory percussion, from left to right in the fifth left intercostal space, the subject detects the change in wave-length when the heart is reached as quickly as does the observer. In this case, the vibrations set in motion by the blow must travel through the chest-wall and a layer of lung to the heart and be reflected back to the pleximeter finger, and the intervention of either touch- or pressure-sense is clearly eliminated. Different subjects have described the sensation when the heart is reached as a slight "shock" or "jar" felt within the chest.

In my opinion, the most significant conclusion reached by any investigator of the vibration sense is Miss Keller's: "every atom

of my body is a vibrascope." This is in agreement with Jennings' statement that the nervous system and sense organs are not necessary for the reception of any particular class of stimuli. All biologists agree that every living cell in the human body retains some of the functions possessed by protozoa; for example, all breathe and carry on their metabolic exchanges, however much these may have been modified. Many cells specialize in a definite function and have completely lost one or more of the others: muscle cells contract but cannot reproduce themselves. On the basis of these considerations and the fact that, during percussion, changes in the frequencies of vibration waves are detected by the heart, the liver, the spleen and that portion of a lung consolidated by pneumonia, I would suggest that the vibration sense is a special sense, mediated by the cells themselves instead of by specialized receptors like those for touch; in other words, the vibration sense is a survival of the sensitivity of protozoa to the coarser vibrations and is retained by all living cells of the body in greater or less degree. If this theory is correct, the vibration sense is independent of the senses of touch, pressure, pain, temperature and deep sensibility.

With this background it is easier to understand the rôle of the vibration sense in percussion. For years it has been recognized that the sound produced during percussion is only one of the elements entering into the interpretation of the results: the other is the way the object "feels." This has been described also as the "sense of resistance" and much significance has always been attached to it. Piorry,[14] who introduced mediate percussion, discussed it. Ebstein[2] published a monograph on *Tastperkussion*. Norris and Landis[12] say that a physician is able to state positively whether a given note is resonant or flat, with his ears closed, simply by his sense of touch; they add that "our judgments are derived from the pressure sense of the skin and the muscle sense." Many other authors have referred to the sensations imparted to the fingers (both pleximeter and plexor) during the act of percussion. But nowhere in the literature, after an extended search, have I been able to find any reference to the relation between the "feel" or resistance of an organ or area and the vibration sense. The vibration sense is in fact a sixth sense that the physician brings, consciously or unconsciously, into the interpretation of physical signs. Laura Bridgman[7] asserted that she "heard" with her feet. Miss Keller "hears" the human voice by placing her fingers on the speaker's lips and throat. In palpation of the chest, as well as in percussion, the physician "hears" with his hand or his fingers.

The vibration sense, it should be pointed out, is capable only of comparing the frequencies of vibrations, not of measuring them. But just as some persons possess the ability of locating on the scale with a fair degree of accuracy the pitch of a sound, so, I believe, clinicians may acquire the ability to recognize through the vibra-

tion sense an abnormal "pitch" on percussion before they compare it with adjacent normal areas. Pitch is translated by the vibration sense into "feel" or resistance. Areas that give a high-pitched sound on percussion "feel" hard or resistant: areas giving sounds of lower pitch "feel" softer. The acuity of the vibration sense was appreciated by Piorry, who stated that the finger that strikes gives as accurate information as the ear that hears. My experience, including the frequent comparison of sound with the sensation in the pleximeter finger in mediate percussion and in the plexor in immediate, is in complete agreement with this conclusion of Piorry.

If I may judge by my observations, years of training are required —self-training for the most part—to understand the true significance of the "feel" or resistance of a region—the sound produced in percussion is emphasized to such an extent. It is easy enough to recognize that a pleural effusion or a lung consolidated by cancer "feels" hard, but the finer distinctions are often overlooked. "Feel" or resistance became clear to me only when I began to estimate it in terms of vibrations and the vibration sense. As I have watched older and more experienced physicians examine patients with apparently unorthodox methods of percussion, I was formerly inclined to be critical, yet I marveled at the accuracy of their diagnoses. In retrospect I doubt whether they themselves realized they were obtaining their information through a special sense. Looking on, I did not know what they were doing. The very fact that experience gradually leads to increased reliance upon the "feel" in percussion gives it special significance and indicates the importance of teaching students percussion in terms of vibrations and the vibration sense as well as in terms of sound.

In concluding this discussion, it may be pointed out that the vibration sense plays a rôle in auscultation only second to that in percussion. The best known illustration of this fact is the occasional case of aortic regurgitation in which the murmur cannot be heard with a stethoscope but is clearly audible when the ear is placed upon the chest, preferably upon the bare skin. Less striking instances occur constantly. My attitude is that it is always necessary in difficult cases to employ immediate auscultation, and that, to acquire familiarity with it, its frequent use is desirable. In immediate auscultation the tissues of the head, including the skin and bones, pick up the vibrations.

Summary. 1. The importance of vibrations in the orientation of animals to their environment is pointed out and studies on the reception of vibrations of different frequencies by certain lower animals are briefly reviewed.

2. Various studies of the vibration sense in man are reviewed, and a new concept of the nature of the vibration sense and how it is mediated, based on experiments in percussion, is presented. According to this theory, the vibration sense is a survival of the sensitivity

of protozoa to the coarser vibrations and is distinct from the senses of touch, pressure, pain, temperature and deep sensibility.

3. The relation of the vibration sense to interpretation of the results of percussion, especially palpatory percussion, is then discussed.

REFERENCES.

(1.) **Cole, F. J.**: Proc. Roy. Soc., **82** (Ser. B), 391, 1910. (2.) **Ebstein, W.**: Die Tastperkussion, Stuttgart, F. Enke, 1901. (3.) **Egger, M.**: J. d. Physiol. et d. Path. Gen., **1**, 511, 1899. (4.) **Evans, H. M.**: Proc. Roy. Soc., Lond., **111** (Ser. B), 247, 1932. (5.) **von Frey, M.**: (*a*) Sitzungsb. d. phys. med. Gesellsch. zu Würzb., No. 3, p. 38, 1915; (*b*) Ztschr. f. Biol., **65**, 417, 1925. (6.) **Gray, R. C.**: Minnesota Med., **15**, 674, 1932. (7.) **Hall, G. S.**: Laura Bridgman, Mind, Quart. Rev. Psychol. and Philos. edited by G. C. Robertson, London, Williams & Norgate, **4**, 149, 1879. (8.) **Herrick, C. J.**: Introduction to Neurology, 5th Ed., Philadelphia, W. B. Saunders Company, 1931. (9.) **Jennings, H. S.**: Behavior of the Lower Organisms, New York, Columbia University Press, 1906. (10.) **Keller, H. A.**: The World I Live In, New York, The Century Company, 1908. (11.) **Manning, F. B.**: J. Exp. Zool., **41**, 5, 1924. (12.) **Norris, G. W.**, and **Landis, Henry R. M.**: Diseases of the Chest, 4th Ed., p. 94, Philadelphia, W. B. Saunders Company, 1929. (13.) **Parker, G. H.**: (*a*) Bull. U. S. Bureau of Fisheries, **24**, 183, 1904; (*b*) Ibid., **30**, 97, 1912. (14.) **Piorry, P. A.**: De la percussion médiate et des signes obtenus à l'aide de ce nouveau moyen l'exploration dans les maladies des organes thoraciques et abdominaux, Paris, J. S. Chaude, 1828. (15.) **Rumpf, —.**:Neurol. Centralbl., **8**, 185, 222, 1889. (16.) **Rydel, A.**, and **Seiffer, W.**: Arch. f. Psychiat., **37**, 488, 1903. (17.) **Symns, J. L. M.**: Quart. J. Med., **11**, 33, 1917–1918. (18.) **Tilney, F.**: Arch. Neur. and Psychiat., **21**, 1237, 1929. (19.) **Treitel, L.**: Arch. f. Psychiat., **29**, 633, 1897. (20.) **Wever, E. G.**, and **Bray, C. W.**: J. Cell. and Comp. Physiol., **4**, 79, 1933–1934. (21.) **Wood, R. W.**, and **Loomis, A. L.**: Philosophical Magazine, **4**, 417, 1927.

SPECIFIC TREATMENT OF PNEUMOCOCCUS TYPE I PNEUMONIA.

INCLUDING THE USE OF HORSE AND RABBIT ANTIPNEUMOCOCCUS SERUMS AND SULPHANILAMIDE.

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THERE has been an unusual increase in interest recently in the methods and results of specific serum treatment of the pneumonias. It is appropriate at this time, therefore, to bring up to date the experience at the Boston City Hospital with the pneumonias due to the more frequent types of pneumococci to which this mode of therapy has been applied. The relative increase in the number of

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cases treated with serum at the hospital and the introduction, during the past year, of antipneumococcus rabbit serum and of sulphanilamide are further reasons for taking stock at this time. The present paper will deal with the cases of Type I pneumonia in adults. Those due to pneumococci of the other common types will be considered in separate communications. We shall consider in detail only the results obtained from 1935 to 1938, the three years that have elapsed since the last report.[7c]

Patients, Materials and Methods. During the past few years, an effort has been made at this hospital to identify the common significant bacterial agents in all adult cases of acute pulmonary infection and also to type every pneumococcus encountered in these or other conditions. Between Sept., 1929, and July, 1938, the Type I pneumococcus was identified in 1125 cases. Table 1 shows the close association of this type with primary lobar pneumonia. Only 57 (5.1%) of all cases harboring Type I pneumococci did not have pneumonia or empyema. In only 14 instances (1.2%) was this organism obtained from the sputum or pharyngeal culture in the absence of pneumonia or empyema. Among the 897 cases of Type I pneumonia in adults, only 34 (3.8%) showed patchy or "atypical" pulmonary consolidation and in many of these the pneumonia was first recognized or the pneumococcus was first typed from autopsy material. More than 80% of these were "secondary," that is, followed injuries or operations or occurred during the course of other serious acute illness or during the end stages of severe chronic diseases. The remaining 863 cases showed typical lobar pneumonia according to the best evidence obtainable from autopsy, roentgenographic or physical findings. Among the latter, less than 7% were secondary.[7a,18b]

TABLE 1.—PATIENTS HARBORING TYPE I PNEUMOCOCCI, 1929–1938.

Adults with lobar pneumonia	863
Adults with atypical pneumonia	34
Adults admitted with empyema	27
Infants and children* with pneumonia and/or empyema	144
Focal infections without pneumonia	43
Carriers or respiratory infections without pneumonia	14
Total number of cases	1125

* Not studied routinely. These types usually obtained from cultures of blood or pleural fluids.

Selection of Cases. During the earlier studies an attempt was made to treat alternate cases with specific serum either as they were encountered[7b] or as the type was determined.[20a] These methods of choosing cases proved to be neither desirable nor workable. It was then deemed best to treat with serum only those patients in whom the type was obtained early in the disease, 96 hours after the onset being chosen, on the basis of previous experience, as the dividing line. However, this was not adhered to very rigidly. As greater supplies of serum became available, this limit was gradually extended until all patients with Type I pneumococcus pneumonia were treated with serum as soon as this type was determined, except: 1, patients already showing evidence of recovery; 2, those in whom focal complications were already established; 3, patients in "collapse" with evidence of circulatory failure or pulmonary edema; and 4, certain doubtful cases in which it was shown that Type I agglutinins were present in the blood or when the immediate skin reaction to Type I specific capsular poly-

saccharide was positive.[21] Some of the patients with focal complications were given serum, however, if the blood culture was positive or if the pneumonia was considered to be still active. Likewise, some of those in "shock" were treated after the "collapse" or pulmonary edema showed evidence of improvement under appropriate measures. Experimental lots of serum were used first to treat younger patients or those who were in good general condition unless no other serums were available at the time.

Serums Used. Some 80 different lots of concentrated antipneumococcus horse serum were used during the last 3 years. These ranged in potency from 1500 to 4500 units per cc.; 15 lots contained less than 2000, 34 contained from 2000 to 3000, and 31 had more than 3000 units per cc. Most of these lots were furnished for clinical trial before they were released for general use, and experimental methods were employed in the concentration of a number of them. Concentrated rabbit serums of five different lots were used, one with 10,000, three with 4500 and one with 1000 units per cc. Several different methods were used in the concentration of these serums. Except for occasional experimental lots, all Type I serums were standardized by the approved National Institute of Health mouse tests in relation to the control serum P11, to which a value of 300 Type I units per cc. was assigned.[6,11] All the rabbit serums and 8 of the horse serums were monovalent. The rest were bivalent and contained Type II antibody. The concentration of the latter in terms of a similar standard unit (P11 = 150 Type II units) was from one-third to the same number of units as Type I. In the text and tables, numbers of units will refer to the actual titrated values in contrast to the values finally placed on the labels, which were usually from 10 to 40% less.

Typing. The Neufeld method[15,19] applied directly to the sputum has been relied on to the largest extent for the original typing upon which therapy was based. In almost every instance this was checked by typing from the peritoneal exudate or heart's blood of a mouse inoculated with the sputum and/or from typical colonies picked off the surface of blood agar plates inoculated with the sputum or with the mouse's exudate or heart's blood. Typing from these materials was done either by macroscopic or microscopic agglutination or by the Neufeld method or by a combination of these methods. The direct sputum typing proved highly efficient. During this last 3-year period, a diagnosis of Type I by this method proved to be wrong, as judged by the results of mouse inoculation of the same material, in only 2% of the sputum specimens. Among the sputa which were examined by both the direct method and by mouse inoculation and which yielded Type I pneumococci from the mouse, this organism was not recognized directly in the sputum in 7% of the specimens. Patients from whom sputum was not obtainable were successfully typed, in most instances, by inoculating pharyngeal swabs into suitable broth containing defibrinated rabbits' blood, incubating for 4 to 6 hours, injecting some of the culture into a mouse and withdrawing peritoneal exudate from the mouse after 3 to 6 hours. Frequently, the broth culture yielded the type directly. Blood cultures were taken frequently during the acute disease and positive cultures were typed directly by the Neufeld or by agglutination methods.

Serum Injections and Dosage. All of the serums were given intravenously except in occasional cases where intramuscular injections were used for investigation or because the reactions from intravenous injections of some experimental serums were too severe to continue by that route. The usual precautions were carried out and included careful history concerning allergic tendencies and previous serum injections. Adrenalin was always made available for immediate use. Intracutaneous, conjunctival and, in some cases, treated with rabbit serum, intravenous tests[9] were performed. Serum was

given to every case regardless of the history or the results of the various tests, these being used only as a guide for extra caution during the injections or for rearranging dosage.

In general, a total initial dose of 60,000 to 80,000 units was given to patients under 30 years, unless it was already known that the blood culture was positive. This dose was increased according to age and also approximately doubled: 1, when more than one lobe was involved; 2, when it was known that the blood culture was positive; 3, in pregnant or recently parturient women; or 4, in acutely ill patients when treatment was begun late in the disease. This predetermined original amount was given in divided doses at 2-hour intervals. The usual initial injections consisted of 1 to 5 cc., the second, 10 to 25, and the later ones, 20 to 45 cc., taking from 10 to 20 minutes for each injection. The serum was warmed to approximately body temperature before the injection and given undiluted, except in occasional instances where it was given in 2 to 10 parts of physiological salt solution.

Sulphanilamide was used only during the last year. Some patients received this drug before the pneumococcus type was determined and its administration was continued with or without serum thereafter. The combination of serum and sulphanilamide was used in some of the cases treated late in the disease, particularly if the blood culture was positive or if purulent complications were present or suspected. The usual routine was to give the drug orally, 2 gm. every 2 to 4 hours for 4 doses, and then 1 gm. every 4 hours. Dosages were changed, as necessary, depending on the course of the disease or the occurrence of untoward symptoms. When the blood values were determined,[14] the doses were regulated in an effort to maintain a level of 10 mg. of the drug per 100 cc. of blood with a daily fluid intake of 3 to 4 liters. After the severe symptoms subsided smaller amounts were used, usually 4 gm. daily, in 4 to 6 doses. Bicarbonate of soda was given with each dose of the drug. The dosage was decreased or discontinued as soon as definite improvement was apparent, except in the presence of purulent complications. The usual precautions were taken and transfusions were used freely in patients receiving this drug over long periods. In the tables that follow, the cases receiving sulphanilamide are not segregated. The effect of this therapy will be considered separately below.

Results. *Mortality.* The crude death rates in the cases receiving specific antipneumococcic serums and in those treated without such serums are shown in Table 2. It is to be emphasized at the outset that we are not dealing with "controls." The non-serum treated cases are included here for comparison mainly because it is desirable to present, as nearly as possible, all the significant data concerning mortality. It will be noted that, although the proportion of cases of Type I pneumonia receiving serum has increased from 43 to 89%, the difference in mortality between the serum treated and non-serum treated cases has remained fairly constant.

Any presentation concerning the mortality from pneumonia is incomplete if it fails to consider the most important factors influencing the prognosis in this disease, namely: bacteremia, age and the presence of systemic complications. When serum is used, the stage of the disease when it is given and the amount are highly important. Each of these factors will be considered in turn.

TABLE 2.—MORTALITY IN CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA.

Years.	Serum treated.			Non-serum treated.			Treated with serum, %
	No.	Died.	Died, %	No.	Died.	Died, %	
1929–35[7c]	219	40	18	289	113	39	43
1935–36	68	12	18	61	27	44	53
1936–37	79	17	22	23	10	43	77
1937–38	93	16	17	12	5	42	89
Total	459	85	19	385	155	40	54

NOTE.—In this table and in those that follow, all cases receiving specific serum are included, regardless of time of treatment, complications or amount of serum. From the non-serum treated cases, those fatal cases in which the type was determined at autopsy were excluded. There were 13 such cases in the years 1929–35, 2 in 1935–36, 5 in 1936–37, and 3 in 1937–38. The 1937–38 serum treated cases include those treated with rabbit serums.

TABLE 3.—INCIDENCE OF BACTEREMIA AND ITS EFFECT ON THE DEATH RATE IN CASES OF TYPE I PNEUMOCOCCUS PNEUMONIA.

Years.	Cases treated with specific serum.							Cases treated without specific serum.						
	Blood cultures positive.			Positive blood cultures, %.	Blood cultures sterile.*			Blood cultures positive.			Positive blood cultures, %.	Blood cultures sterile.*		
	No.	Died.	Died, %.		No.	Died.	Died, %.	No.	Died.	Died, %.		No.	Died.	Died, %.
1929–35	69	25	36	32	150[27]	15[9]	10	100	81	81	34	189[69]	32[8]	17
1935–36	25	11	44	37	43	1	2	30	20	67	49	31[7]	7[3]	23
1936–37	33	12	37	42	46	5	11	7	5	71	30	16[1]	5[0]	31
1937–38 Horse	33	10	30	43	44	4	9	3	3	100	25	9[7]	2[1]	22
1937–38 Rabbit	7	1	14	44	9	1	11							
Total	167	59	35	36	292[27]	26[9]	9	140	109	78	35	245[79]	46[12]	19[17]

* Includes cases in which blood cultures were not done. The numbers of such cases are indicated in the superscripts.

Bacteremia (Table 3). It has previously been shown that treatment with specific serum either prevents the occurrence of bacteremia or clears the blood stream of bacteria in most cases where invasion has already taken place. It is not surprising, therefore, that the incidence of bacteremia among the serum treated cases increased during the past 3 years as relatively more of the severely ill patients were treated late in the disease. The death rates among both the bacteremic and non-bacteremic serum treated cases remained relatively low, as compared with the corresponding non-serum treated cases. The death rate among the bacteremic cases treated with rabbit serum appears to be comparatively low, but the number of cases is small and the age of the patients more favorable, as will be seen below.

There was an opportunity during these 3 years to observe the

results of more than one blood culture taken before beginning serum treatment in 27 bacteremic cases. In 19, all these cultures were positive and in 8 the earlier cultures were sterile and the one taken before the initial dose of serum was positive. The reverse was not observed in any serum treated case. After treatment, blood cultures became and remained sterile in 13 fatal bacteremic cases. In only 1 case were sterile blood cultures obtained before treatment and positive cultures later. This patient had empyema and extreme leukopenia. Among the non-serum treated cases the blood cultures were repeatedly positive in 11 cases, but 7 had sterile blood cultures first and then developed bacteremia while under observation.

TABLE 4.—INFLUENCE OF AGE, SPECIFIC SERUM THERAPY AND BACTEREMIA ON DEATH RATES. PNEUMOCOCCUS TYPE I PNEUMONIA. 1935–38.

Age group, yrs.	Cases treated with specific serum.*							Cases treated without serum.						
	Blood culture.				All cases.			Blood culture.				All cases.		
	Positive.		Negative.					Positive.		Negative.†				
	No.	Died.	No.	Died.	No.	Died.	Died, %.	No.	Died.	No.	Died.	No.	Died.	Died, %.
12–19	8^{2}	1	23^{8}	0	31^{8}	1	3	2	0	4	0	6	0	0
20–29	14^{1}	2	37	0	51^{1}	2	4	1	0	14^{2}	1	15	1	7
30–39	27^{1}	9	38^{1}	3^{1}	65^{2}	12^{1}	18	9	5	13^{2}	2^{1}	22	7	32
40–49	22^{1}	5^{1}	32^{1}	4	54^{2}	9^{1}	17	13	10	5^{1}	0	18	10	56
50–59	14^{2}	8	8	2	22^{2}	10	45	7	6	12^{2}	6^{1}	19	12	63
60–69	9	5	4^{1}	2	13^{1}	7	54	6	5	4^{1}	2^{1}	10	7	70
70+	4	4	..	..	4	4	100	2	2	4^{1}	3^{1}	6	5	83
Total	98^{7}	34^{1}	142^{9}	11^{1}	240^{16}	45^{2}	19^{15}	40	28	56^{10}	14^{4}	96	42	44
	35% died		8% died					70% died		25% died				

* Includes cases treated with rabbit serums. The superscripts indicate the numbers so treated.
† Includes cases in which blood cultures were not done, the numbers of which are indicated by superscripts.

Influence of Age. In Table 4, the serum treated and non-serum treated cases occurring during the last 3 years are listed according to age and the results of blood cultures. The expected increase in death rate with advancing age is apparent in each instance. It would appear from these data that the greatest reduction in death rate from the use of serum occurred under the age of 50, although the basis for comparison is not entirely satisfactory in every age group. There may also have been some reduction in death rate among the treated cases in the sixth and seventh decade in spite of the relatively greater number of bacteremic cases treated. It is evident, from the manner in which cases were chosen for treatment, that relatively few severely ill patients in the younger age groups failed to receive serum. This may serve to explain the unusually low death rates among the non-serum treated cases in the second

and third decade, most of these cases having recovered at the time the type was determined.

Effect on the Death Rate of the Day of the Disease When Treatment is Begun. It was previously noted[7c] that the death rate was considerably greater in cases of pneumococcus Type I pneumonia treated with specific serum after the fifth day of the disease than in those cases treated on the fifth day or earlier. When the experience of the last 3 years is added, the accumulated data indicate that there is a gradual increase in death rate after the fourth day, the greatest increase occurring after the sixth day (Table 5). Similar differences are noted in both bacteremic and non-bacteremic cases.

TABLE 5.—INFLUENCE OF THE DAY OF THE DISEASE WHEN SPECIFIC SERUM TREATMENT IS BEGUN ON THE DEATH RATE IN CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA.

Day treatment begun.	Years.	Blood culture positive.			Blood culture sterile or not done.			All cases.		
		No.	Died.	Died, %	No.	Died.	Died, %	No.	Died.	Died, %
Fourth day or earlier	1929–35	37	11	30	95	6	6	132	17	13
	1935–38	61	16	26	118	6	5	179	22	12
	1929–38	98	27	*28*	213	12	*6*	311	39	*13*
Fifth day	1929–35	12	3	25	25	2	8	37	5	13
	1935–38	14	6	43	12	3	25	26	9	35
	1929–38	26	9	*35*	37	5	*13*	63	14	*22*
Sixth day	1929–35	6	3	50	15	3	20	21	6	29
	1935–38	11	4	36	8	1	13	18	5	28
	1929–38	17	7	*41*	23	4	*17*	39	11	*28*
Seventh day or later	1929–35	14	8	57	15	4	27	29	12	42
	1935–38	12	8	67	4	1	25	16	9	56
	1929–38	26	16	*62*	19	5	*26*	45	21	*47*

Dosage. The general scheme according to which the doses were arranged has been mentioned. During 1936–37 relatively small doses were used, as recommended in the Massachusetts Pneumonia Program, namely, 60,000 units for the initial dose in all patients, regardless of age.[12] During the following year the initial dose was gradually increased except in the younger patients. Larger initial doses were given throughout this period under the conditions mentioned above and treatment was continued if the therapeutic response was not adequate. The average doses used during each of the 3 years are summarized in Table 6. Smaller amounts of rabbit serums were used chiefly because during this period these serums were treated as experimental and were given chiefly to younger patients or to those in the best general condition and with relatively milder disease. The average dose of antibody was increased considerably during these 3 years, particularly in the older patients and in those with positive blood cultures.

TABLE 6.—ANALYSIS OF AVERAGE DOSES PER PATIENT OF PNEUMOCOCCUS TYPE I ANTIBODY. 1935–38.*

	1935–36.	1936–37.	1937–38. All cases.	1937–38. Horse serum.	1937–38. Rabbit serum.
Volume, cc.	44	52	81	93	23
Units† (thousands)	101	138	200	214	129
Units per cc.	2270	2650	2470	2300	5610
Number of injections	3.5	3.9	5.3	5.8	2.6
First injection (thousands of units)	5	9	7	7	21
Subsequent injections	38	44	45	43	68
Total dose per patient:					
Recovered cases	97	132	185	214	124
Fatal cases	119	162	269	284	165
Non-bacteremic cases	87	114	144	152	105
Bacteremic cases	125	170	273	300	160
Age group: 12–19 years	96	100	126	158	94
20–29 years	99	120	171	172	150
30–39 years	109	149	186	180	203
40–49 years	108	128	227	239	100
50–59 years	88	149	240	254	178
60–69 years	55	152	278	293	200
70 years and older	..	173	415	415	
Average age (years)	34.4	37.5	36.8	38.2	30.2

* For the years 1929–35 (7[6]) the average amount of serum used per patient was 94 cc., containing 147,000 units or 1560 units per cc.

† The number of units given on the labels was 10 to 40% lower than these actual values obtained on standardization.

Untoward Reactions. The numbers of cases exhibiting various reactions are listed in Table 7. It will suffice to mention some of the interesting features of the reactions in each of the main groups.

TABLE 7.—OCCURRENCE OF UNTOWARD REACTIONS IN CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA TREATED WITH CONCENTRATED SPECIFIC ANTIBODY. 1935–38.

	Horse serums (224 cases).	Rabbit serums (16 cases).
Immediate reactions	21 (9%)	0
Nausea and vomiting after one or more doses	7	
Urticaria	6	
Palpebral edema and asthma	1	
Dyspnea and wheezing (asthma)	6	
Fainting	1	
Delayed serum sickness	52 (23%)	5 (31%)
Fever alone	5	1
Arthralgia	28	1
Urticaria	7	0
Arthralgia and urticaria	12*	3
Thermal reactions	66 (31%)	7 (44%)
Single chill	45	5
Chill after each of 2 injections	17	2
Chill after each of 3 injections	4	
Only after initial injection	10	3
After initial and later injection	16	2
Only after second and/or later injections	40	2
Lederle serums supplied for clinical trial (74 cases)	6 (8%)	
State supply† (150 cases)	60 (40%)	
1935–36 (63 cases)	25 (40%)	
1936–37 (32 cases)	3 (9%)	
1937–38 (55 cases)	32 (58%)	

* Two of these patients had asthma during this attack, 1 had enlarged nodes, 1 had purpura and thrombopenia, and 1 had 2 bouts one week apart.

† Including some used for clinical trial.

Immediate Reactions. Nausea and vomiting and vague pains and discomforts usually followed the injection of lots of serum which gave thermal reactions, frequently, in the same or in other patients. Among the 6 patients who had urticaria soon after receiving serum, this reaction occurred after the first dose in 1 case, after the second dose in 1, after the third in 2 cases, after the third and fourth doses in 1, and only after the fourth injection in 1 case. Only 2 of these 6 patients gave positive skin tests for horse serum and one other had a history of previous serum injection (tetanus antitoxin). Palpebral edema, asthma and fainting occurred only in patients with a personal or familial history of asthma. Only 2 patients among those exhibiting immediate reactions later had serum sickness. The large majority of the patients with a history of allergic manifestations or of previous serum injections, as well as those giving positive skin tests, had no immediate reactions following the therapeutic injections.

Thermal Reactions. These usually consisted of mild chills occurring almost uniformly about 1 hour after the injections and were followed by rises in fever of 1 to 4° F. They were less common after the small initial doses of 2 to 5 cc. In some patients the first chill occurred after the fourth or even a later injection which was no larger, and sometimes even smaller, than the preceding injections of serum of the same lot. Chills have occurred in many instances in spite of the use of generous doses of aspirin prior to the injection (used during 1937–38). It is possible, however, that some chills may have been averted or were less severe when this drug was used. While the large majority of patients suffered no serious consequences from these chills and, in fact, often had an exaggerated sense of well-being following them, they were sometimes distinctly harmful. In elderly or debilitated individuals and in other severely ill patients treated late in the disease, even mild chills were followed by a seemingly premature development of circulatory collapse and/or pulmonary edema and a fatal issue may have been hastened in this manner. Similar episodes occasionally followed the more severe reactions in younger individuals who were in good general condition. Such severe reactions were observed in 1 patient treated with horse serum and in 2 patients treated with experimental lots of rabbit serum. All 3 were resuscitated after vigorous treatment for the hyperpyrexia and the generous use of stimulants. Chills were unusually frequent with the serums recently supplied by the State Laboratory, but this varied in different years.

Serum Sickness. The incidence of serum sickness among the cases treated with horse serums was 23% and was almost exactly the same in each of the last 3 years. It was also the same among the cases treated with the Lederle serums as among those treated with the serums provided by the state, although these serums differed in their chill-producing properties. The symptoms of

serum sickness were almost always mild. In only 2 cases was the arthralgia severe and difficult to control with ordinary analgesic drugs. The urticaria was easily relieved by small doses of adrenalin. The symptoms usually lasted from a few hours to 3 days.

Clinical Response. The character of the symptomatic response to serum therapy during the past 3 years was similar to that previously noted.[7c] Among the 195 recovered cases, 159 (82%) were afebrile and free of symptoms of the acute disease within 48 hours after the first injection of serum, and 109 (56%) had passed the crisis within 24 hours.

Empyema developed in 21 (11%) of the serum treated patients who recovered. Of these, 17 had positive blood cultures before treatment representing 26% of the serum treated bacteremic survivors, and 4 had sterile blood cultures, or 3% of the non-bacteremic cases who recovered after serum treatment. The latter 4 patients were all treated on the fourth day. In 1 of these cases the fluid was sterile after the first tap and resorbed spontaneously. A second had a putrid empyema complicating a lung abscess and no pneumococci could be cultured from the pleural fluid. Among the bacteremic patients who developed empyema, serum treatment was begun on the second day in 1 patient (this patient received only 100,000 units of which the first 60,000 were given intramuscularly), on the third day in 2, on the fourth in 6, on the fifth in 3, on the sixth in 4 and on the seventh in 1 patient. Rabbit serum was used in the treatment of 3 of these cases, including one who received only 90,000 units intramuscularly on the fourth day and 2 who received 250,000 and 300,000 units, respectively, on the third and sixth days. Surgical drainage was employed in the treatment except in the patient mentioned above whose fluid became sterile and resorbed spontaneously and one of the rabbit serum recipients who was treated by repeated thoracentesis over a period of 6 weeks.

Other Complications in Recovered Cases. Sterile effusions were demonstrated in 10 serum treated cases. All the 10 patients were treated before the fourth day and the fluid resorbed spontaneously in each instance. Only 1 of these patients had a positive blood culture; this patient received 180,000 units on the second day of the disease. *Septic parotitis* developed during convalescence in 3 of the non-bacteremic serum treated cases, but no pneumococci could be cultured from the parotid pus in any instance. Two bacteremic patients treated after the seventh day developed abscesses of the leg from which Type I pneumococci were cultured. One of the patients with empyema also had purulent subdeltoid bursitis (and arthritis) with Type I pneumococci in the exudate.

Among the 54 non-serum treated patients who recovered, empyema developed in 6 (11%), including 3 of the 12 bacteremic and 3 of the 42 non-bacteremic cases. Sterile effusion was demonstrated

in 1 case and otitis media and mastoiditis occurred in another. The blood cultures were sterile in the 2 latter cases.

Fatal Cases. Since none of the specifically treated cases have been excluded in determining the death rates given in the various tables, it will be of interest to note briefly some of the factors contributing to the fatal outcome in the individual cases. Multiple factors were operative in many of the cases but only the most important ones will be mentioned.

There were 15 cases in which the pneumonia occurred as a complication of other serious disease. These included: diabetic coma 2, uremia 1, decompensated valvular rheumatic heart disease 3, arteriosclerotic heart disease with auricular fibrillation and failure 3, cerebral thrombosis with hemiplegia 1, induced abortion with overdose of ergotamine 1, massive hemorrhage with severe anemia 2, prostatic obstruction with peripheral neuritis and later parotitis 1, and lung abscess following tonsillectomy 1. In 4 patients death was probably due to superinfection. These included: 1 with mediastinitis and 1 with pericarditis, each due to hemolytic streptococci, and 2 patients in whom Type I pneumococci were found only in the first sputum and later ones showed only hemolytic streptococcus in the one and Staphylococcus aureus in the other. Purulent pericarditis was present in 3 cases (1 also had vegetative endocarditis) at the time treatment with serum was begun. Although many alcoholic patients are included among both the recovered and the fatal cases, there were 5 in whom the alcoholism was probably a major factor in the fatal outcome. Two of these patients were admitted in deep alcoholic coma from which they were never completely roused and 3 had very active delirium tremens which resisted all measures, and death occurred suddenly during violent muscular hyperactivity after apparently good response to serum. There were 9 patients whose general condition at the time the type was determined was so poor that vigorous measures had to be taken to combat peripheral vascular collapse and pulmonary edema before treatment with serum could be undertaken or carried through. In some of these cases it was considered unwise to continue with serum treatment after the first or second injection even when untoward reactions were not manifest. In 3 other patients treatment was inadequate for other reasons. One of these was thought to be Type II on the basis of the Neufeld typing, was treated vigorously with serum for this type until bacteremia developed and Type I was obtained from the blood culture. At this time the patient was *in extremis* and only one dose of Type I serum could be given before he expired. The second patient was given a total of 100,000 units although bacteremia and massive empyema were present at the time. The third was a bacteremic patient who received 75,000 units each on the fourth and fifth day during which the pulmonary lesion extended and then meningitis developed in

spite of further doses of 100,000 units during each of the next 2 days. Finally, there were 3 patients with sterile blood cultures before serum treatment, who were apparently improved following a moderate dose but suddenly became worse. One of these had a large empyema and leukopenia and later developed bacteremia.

Cases Treated With Rabbit Serums. (See Tables 3, 4, 6 and 7.) It has already been noted that, owing to the experimental nature of these serums, they were first used in the treatment of younger adults and in others who appeared to be in good general condition. Various experimental methods were used in the concentration of these serums. Of the 16 patients with pneumococcus Type I pneumonia treated with these rabbit serum concentrates, 2 died. Blood cultures were positive before treatment in 7 patients, of whom 1 died. This was a 56-year-old patient treated on the fifth day of the disease. He was in mild circulatory collapse at the time and became comatose after only 2 doses containing 55,000 units had been given and died 17 hours later. Autopsy revealed bilateral atypical pneumonia with empyema and purulent pericarditis. Empyema developed in 3 of the bacteremic survivors. One of the patients, a 14-year-old boy, received only a single intramuscular injection of 90,000 units on the fourth day and felt sufficiently improved in 12 hours so that no further specific therapy seemed indicated. The non-bacteremic patient who died had 4 other "higher" types of pneumococci in his sputum in addition to the Type I, but culture of the sputum before death showed an almost pure growth of Staphylococcus aureus. This patient and 1 of those with empyema also received sulphanilamide and are listed below (Cases 7 and 11, respectively, in Table 8).

The clinical response in the patients who recovered was similar to that observed in cases treated with horse serum. In 6 cases, including 1 with empyema, crisis occurred in less than 24 hours, in 4 it occurred between 36 and 48 hours, and in 2 it was delayed more than 48 hours after the first dose of serum.

The average amount of antibody per patient was considerably less than in the cases treated with horse serum and, owing to the higher average concentration of the antibodies, the volume injected was much smaller (Table 6). This was probably related, in large part, to the choice of cases. There were no immediate reactions of the "allergic type" (urticaria, asthma, etc.) observed following the injections of rabbit serums, but thermal reactions and serum sickness were somewhat more frequent than among the horse serum recipients (Table 7).

Cases Treated With Sulphanilamide. In general, the cases of Type I pneumococcus pneumonia selected for treatment with sulphanilamide alone, or combined with specific serum were severe cases, seen late in the disease, particularly those with positive blood cultures, or cases with focal or systemic complications or with

mixed infections. In some cases the drug was given only after the latter conditions became evident. The more pertinent data in these cases are listed in Table 8.

TABLE 8.—RÉSUMÉ OF CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA RECEIVING SULPHANILAMIDE WITH OR WITHOUT SPECIFIC SERUM. 1937–38.

Case.	Sex and Age.	Blood cultures.	Lobes involved.	Specific serum.		Sulphanilamide.			Termination: mode, day.	Remarks, complications.†
				Day begun.	Units × 1000.	Days given.	Total, gm.	Mg./100 cc. in blood.‡		
			SERUM-TREATED CASES.							
1	M 30	Pos. 4, 6, 8; Neg. later	Rl	7	650	8–21	84	2.5; 1.7	L8–12	2 transfusions; leg abscess drained 22d day.
2	F 38	Pos. 6; Neg. later	Lu	7	140	7–14	36	9.1	C8	Sulphanilamide continued after crisis.
3	F 19	Neg. 4, 5	Ru	4	340	4–5	6	..	C5	Normal premature delivery 1 month later.
4	M 69	Pos. 8; Neg. 9, 10, 11	RlLl*	8	300	9–14	32	9.0	D14	Cerebral thrombosis preceded pneumonia.
5	M 43	Pos. 10 (?); Neg. later	Lu	10	280	10–36	90	..	L24	Phlebitis; leg abscess drained 12th day.
6	M 44	Pos. 5, 6; Neg. 2, 3, 8, 12	Ru	6	400	6–24	80	3.6; 4.6	L8–9	Some pulmonary edema before treatment.
7	M 33	Neg. 3–8	Ruml	3	R270	6–10	16	..	D10	Staph. aureus predominating in sputum.
8	M 74	Pos. 4; Neg. later	Rl	4	280	16–19	15	..	D19	Improved after serum; drug given for parotitis.
9	F 32	Neg. 7	Ruml	7	200	7–8	8	..	D8	Mild collapse and auricular fibrillation before treatment.
10	F 23	Pos. 4, 5; Neg. later	RulLl	4	550	8–12	20	7.6	L12	Otitis media (strep.).
11	M 57	Pos. 6, 7; Neg. later	Ruml	6	R300	6–13	44	3.8; 5.6	Emp.	Transfusions 13th and 20th days.
12	F 46	Neg. 5, 8, 14	Ruml	5	150	5–14	74	10.4	L13	Transfusion 14th day.
13	M 43	Pos. 5, 11, 13; Neg. 6–10	RlLl	5	540	8–19	73	..	D19	Delirium tremens; endocarditis (?).
			NON-SERUM TREATED CASES.							
14	M 19	Neg. 4, 5, 7	Ll	..	..	6–11	32	..	C7	Drug continued after crisis.
15	M 71	Pos. 7, 8, 9	RulLl*	..	..	7–9	18	..	D9	Cardiac decompensation; auricular fibrillation.
16	M 66	Neg. 18 and autopsy	Ruml	..	..	18–24	64	..	D25	Strep. and Pn. XIII (sputum); empyema and pericarditis (Pn. I).
17	M 62	Neg. 3, 5, 6, 7	Ruml	..	..	6–9	22	..	D9	Extended Rml, 6th day.
18	M 40	Neg. all	RlLu	..	..	30–38	32	..	D48	Emp. neg. first, then strep. and fusiform bacilli; rib resection.

* Atypical consolidation.

† Anemia with a drop of more than 20% hemoglobin occurred in Cases 1, 4, 11 and 13 and a papular rash developed in Case 12.

‡ Unheated (14).

ABBREVIATIONS: Sex: M = male, F = female. Lobes: R = right, L = left, u = upper, m = middle, l = lower. Blood cultures: Pos. = positive for Type I pneumococcus. Neg. = negative; the numerals represent days of disease. Termination: C = crisis, L = lysis, D = died. Specific serum: Units = compared with the National Institute of Health Standard serum, P11, to which a value of 300 Type I units is assigned. R = rabbit serum.

Among the 5 cases treated with the drug but without serum, bacteremia was present in 1, and was not affected by the drug. In the other 4 cases, all blood cultures were sterile in spite of a fatal outcome in 3 of them. In fact, the only patient who recovered was a young, non-bacteremic patient treated late in the disease in whom crises occurred within a few hours.

The combined treatment was used in 13 patients. The average age of these patients was 42.4 years; the average amount of antibody used was 338,000 units per patient, and of sulphanilamide 44 gm., the latter given over an average of 7 days. Blood cultures were positive before treatment in 9 of these cases. In Case 1, the blood culture was still positive after the first course of treatment with serum alone but became and remained sterile after sulphanilamide and more serum were given. In Case 11, the blood culture remained positive after 1 day of the combined therapy. In 4 of the remaining bacteremic cases all the blood cultures were sterile after treatment with serum given alone or with the drug. In Case 13, however, 5 daily blood cultures were sterile after treatment was begun, but 2 cultures taken later again showed Type I pneumococci. This patient developed a cardiac murmur and probably had vegetative endocarditis, but embolic phenomena were not recognized and autopsy could not be obtained to confirm this diagnosis. In only 2 of these 13 cases was a good clinical response rapidly obtained (Cases 2 and 3).

Discussion. Data presented confirm numerous previous observations by many physicians that specific antibody is a highly effective curative agent in the treatment of pneumococcus Type I pneumonia, especially when used early and in adequate amounts.[1,3–5,7,12,17,18,20] In the present cases, as in other similar groups, the deaths have been limited, for the most part, to well-defined groups of cases, namely, those with severe systemic disease, or with other complicating infections, those given inadequate amounts of antibody or in whom the treatment was begun late in the disease in the face of impending circulatory collapse or pulmonary edema or in the presence of serious focal complications.

While many new forms of physical, chemical and biologic agents are advocated from time to time as panaceas in the treatment of pneumonia, none thus far proposed is so thoroughly supported by both experimental and clinical evidence as is the use of specific antibody in cases due to Type I pneumococcus. Two recent important advances in therapy, however, warrant special consideration, namely, specific antibody produced in rabbits[9,10] and the recent chemotherapeutic agents as exemplified by sulphanilamide. It would be out of place to consider here the theoretical considerations which prompted the clinical trial of antipneumococcus rabbit serums[10] or the experimental basis for anticipating beneficial results from the use of sulphanilamide.[2,8,16] We are concerned, at the moment, with an evaluation of the practical clinical results.

Since the comparative studies of horse and rabbit serums were made primarily with Type I antipneumococcus serums and since more clinical data are available for this than for any other type, it is reasonable to attempt first a comparison of results in cases due to this type. A critical consideration of the data presented makes

it obvious that such a comparison will be difficult until a considerably larger number of cases are treated with rabbit serum under conditions similar to those prevailing in the cases treated with antibody produced in horses. For that purpose all the significant data concerning both the antibody and the patients should be available for comparison.

The number of cases treated with rabbit serums in this present series is small, but they bring out several important features. *Concentrated* antibody was used and administered with ease and safety. No doubt additional experience will reduce the hazards still further. Indeed, the more recent lots of concentrated rabbit serums have given no more frequent thermal reactions than most similar horse serums. The immediate type of "allergic" reactions (urticaria, asthma, etc.) have been less frequent with rabbit serums, as might be expected. Thermal reactions and delayed serum sickness, however, are no less frequent either in this series or with the unconcentrated serums used elsewhere.[9,13] It is already evident from the combined experiences now available[9,13] that empyema does occur even when adequate amounts of rabbit serum antibody are used and that the incidence of this complication is probably no less frequent that in cases treated with horse serums.

As to the comparative amounts of antibody, in terms of volume or of units, that are necessary to produce optimum clinical results, it is still more difficult to draw conclusions. Although the cases were not entirely comparable, the dosage of rabbit serum used in our small series was appreciably smaller than the average dose of horse serum. The latter, in turn, is considerably smaller, both in volume and number of units, than the average amount of unconcentrated rabbit serum used at the Rockefeller Hospital[9] or by Loughlin *et al.*[13] The experience with horse serums has been sufficiently convincing with regard to the superiority of concentrated over unconcentrated serums that the use of the latter has been practically abandoned. It seems to us that the aim should be to produce the most potent concentrates that can be given with the least untoward effects unless it can be shown, with reasonable certainty, that there are effective agents in the unconcentrated serums which cannot be retained by proper concentration.

The death rates in the cases treated with rabbit serum both here and elsewhere indicate the striking benefits of this agent. However, they cannot be interpreted as indicating any superiority over concentrated antibody produced in horses. Thus, although there was only 1 death among 25 rabbit serum treated cases reported from the Rockefeller Hospital, no deaths were noted from the same number of cases treated with concentrated horse serums in the same hospital during the preceding 2-year period. In the 28 cases reported by Loughlin *et al.*[13] the death rate was 10.7%. These authors, however, excluded from their series those patients "for

whom serum was used as an auxiliary therapeutic measure and who at autopsy showed disease processes of themselves lethal." The number and character of these cases are not detailed. In the present series of cases it is possible to reduce the death rate in the cases treated with horse serum to as low as 3%, depending on which of the fatal cases one chooses to exclude on similar grounds.

At the moment, it is fair to conclude only that type-specific pneumococcus antibody produced in both horses and rabbits are highly effective curative agents. Perhaps the greatest advantage of Type I antipneumococcus rabbit serum is that it can be given without immediate "allergic" reactions to certain sensitive patients, particularly those who have previously received injections of horse serum.

It is natural that, where an effective specific agent is available, the use of non-specific agents like sulphanilamide should be reserved only for special groups of cases. The bacteriostatic action of this drug may be used for the purpose of enhancing the action of specific antibody[2,8,16] and may prove useful where bacteremia is present late in the disease at a time when antibody itself is likely to be less effective. It may be particularly useful in the treatment of superinfections with hemolytic streptococci which often vitiate the good specific effects of antipneumococcic serums.

The cases in which we used the drug were of the sort that are most likely to be chosen for this therapy. No definite conclusions can be drawn from so small a group; but it would seem that, considering the very poor prognosis in those patients given the combined treatment, the drug was beneficial when used in this manner. By itself, however, it was not very effective. To be sure, in 3 of the fatal cases, it may have prevented the occurrence of bacteremia or at least made it difficult to demonstrate the bacteria in the blood stream by the usual methods. However, it did not readily clear the blood stream of Type I pneumococci in the case in which it was used after invasion had already occurred. In 1 of the cases, bacteremia recurred in spite of the combined treatment. Focal infections harboring large numbers of Type I pneumococci were demonstrated during life or at autopsy after several days of treatment with this drug alone or with specific antibody. These facts would indicate that the drug, at least in the manner in which it was used, was not regularly effective in helping to rid the body of this organism. It is possible that larger doses, more carefully controlled to maintain higher concentrations in the blood, would be made effective. It has been difficult to maintain high levels in pneumonia patients with oral doses that are usually considered adequate.

The introduction of large numbers of new chemotherapeutic agents makes it increasingly difficult to obtain proper clinical evaluation. A word of caution concerning their use in cases of pneumonia or other pneumococcic infections may be in order. In

undertaking clinical trials, the non-specific character of the action of these drugs may be taken by clinicians as an excuse for omitting adequate bacteriologic controls. Such omissions would make it impossible properly to estimate their value in these conditions.

Summary and Conclusions. The death rate among cases of Type I pneumococcus pneumonia treated with concentrated type-specific antibody at the Boston City Hospital has been regularly one-half or less that of similar contemporaneous non-serum treated cases. This has remained true in recent years in spite of the fact that the proportion of cases treated with serum has increased from 43 to 89%. In the cases treated with serum before the end of the fourth day the death rate is less than one-third of the non-serum treated mortality.

Bacteremic and non-bacteremic cases are equally influenced. The greatest reduction in death rate occurs in patients under 50, but those of other age groups are probably also beneficially affected by serum treatment. Empyema occurred after serum treatment chiefly in bacteremic patients, and its frequency was proportional to the delay in beginning treatment.

Type I antipneumococcus serums produced in both horses and rabbits were potent and effective. There are insufficient data to indicate any superiority of the one over the other. There were no immediate allergic type of reactions observed in the rabbit serum recipients, but thermal reactions and serum sickness were somewhat more frequent among them.

Sulphanilamide in the small number of cases in which it was used alone or with serum seemed to influence the course of Type I pneumococcus pneumonia only slightly, if at all.

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REFERENCES.

(1.) **Abernethy, T. J.**: New York State J. Med., **36**, 627, 1936. (2.) **Branham, S. A.**, and **Rosenthal, S. M.**: Public Health Repts., **52**, 685, 1937. (3.) **Bullowa, J. G. M.**: The Management of the Pneumonias, New York, Oxford University Press, 1937. (4.) **Cecil, R. L.**, and **Plummer, N.**: J. Am. Med. Assn., **95**, 1547, 1930. (5.) **Cole, R.**: Ibid., **93**, 741, 1929. (6.) **Felton, L. D.**, and **Stahl, J. H.**: Nat'l Inst. Health Bull., No. 169, 1937. (7.) **Finland, M.**: (*a*) Ann. Int. Med., **10**, 1531, 1937; (*b*) New England J. Med., **202**, 1244, 1930; (*c*) Am. J. Med. Sci., **192**, 849, 1936. (8.) **Finland, M., Brown, J. W.**, and **Rauh, A. E.**: New England J. Med., **218**, 1033, 1938. (9.) **Horsfall, F. L., Goodner, K.**, and **MacLeod, C. M.**: New York State J. Med., **38**, 245, 1938. (10.) **Horsfall, F. L., Goodner, K., MacLeod, C. M.**, and **Harris, A. H.**: J. Am. Med. Assn., **108**, 1483, 1937. (11.) **Kirkbride, M. B., Hendry, J. L.**, and **Murdick, P. P.**: Am. J. Hyg., **23**, 187, 1936. (12.) **Lord, F. T.**, and **Heffron, R.**: Pneumonia and Serum Therapy. New York, The Commonwealth Fund, 1938. (13.) **Loughlin, E. H., Bennett, R. H.**, and **Spitz, S. H.**: J. Am. Med. Assn., **111**,

497, 1938. (14.) **Marshall, E. K., Jr.**: J. Biol. Chem., **122**, 263, 1937. (15.) **Neufeld, F.**, and **Etinger-Tulczynska, R.**: Ztschr. Hyg. Infektionskr., **2**, 492, 1931. (16.) **Osgood, E. E.**: Arch. Int. Med., **62**, 181, 1938. (17.) **Rogers, E. S.**, and **Gooch, M. S.**: New York State J. Med., **38**, 1369, 1938. (18.) **Ruegsegger, J. M.**, and **Benjamin, J. E.**: J. Med., **19**, 168, 1938. (19.) **Sabin, A. B.**: J. Am. Med. Assn., **100**, 1584, 1933. (20.) **Sutliff, W. D.**, and **Finland, M.**: (*a*) J. Am. Med. Assn., **96**, 1465, 1931; (*b*) New England J. Med., **210**, 237, 1934. (21.) **Tillett, W. S.**, and **Francis, T.**: J. Exp. Med., **50**, 687, 1929.

SULPHANILAMIDE IN THE TREATMENT OF GONOCOCCAL ARTHRITIS.

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There are now a large number of reports dealing with the effect of sulphanilamide in the treatment of local gonococcal infections, including urethritis, pelvic inflammatory disease, and ophthalmia. In a discussion of the pathogenesis of gonococcal arthritis and the mode of recovery, together with its treatment, Keefer and Spink[7a] called attention to the fact that sulphanilamide was capable of sterilizing the synovial fluid within a short time after its exhibition by mouth.

More recently, we have found that when sulphanilamide is added to whole blood, or is given by mouth so that it is present in the plasma, the bactericidal power of the blood increases. We have also shown that the bactericidal power of the synovial fluid increases following its use and gonococci may be killed off rapidly in its presence. For these reasons we have studied the effects of sulphanilamide in a group of 14 cases of gonococcal arthritis.

Before presenting our results it is well to review a few of the salient facts concerning gonococcal infection of the joints. From our studies[2a,7a,b,d] it is convenient to divide the cases into three groups on bacteriologic and immunologic grounds: 1, Cases with a local lesion, bacteremia, and metastases in the joints from which organisms can be obtained; 2, cases with a local lesion, sterile blood, and infected joints; 3, cases with a local lesion, sterile blood, and sterile synovial fluid.

When the first group of cases is studied immunologically it is found that the blood and synovial fluid contain no demonstrable

antibodies, but when the blood is cleared of organisms antibodies can be demonstrated therein.

Recovery occurs when the blood and synovial fluid are sterilized and the damage caused by the organisms and their products has been repaired. Such an illustrative case was reported in a previous paper.[2b]

In the second group of cases, namely, those with a local lesion having no evidence of bacteremia, but with infected synovial fluid, there are antibodies in the blood against the homologous strain of organisms but none in the synovial fluid.[2a] The synovial fluid is sterilized when the antibodies increase so that they are present in excess.

In the third group, there are two subdivisions: *a*, Cases with a local lesion, no bacteremia, and sterile synovial fluid, with antibodies of relatively high titer in the blood and synovial fluid; *b*, cases with a local lesion, no bacteremia, sterile synovial fluid, and no demonstrable antibodies in either the blood or synovial fluid. The former is the common finding, the latter is an uncommon occurrence but of great interest and significance. From these cases it might be argued that some of them are not due to gonococcus infection. However, the clinical course and the subsequent appearance of antibodies in these patients are strong points in favor of the diagnosis of gonococcal arthritis. The observations of Ralston[6] on the effects of gonococcal toxins or sterile autolysates (Corbus-Ferry filtrate) are of great significance in understanding the possible origin of this type of arthritis. It is known that these products are exceedingly histiotoxic for skin, the urethra, and the joints; and when this material, which is antigenic, is injected into horses, the commonest finding is the development of an acute polyarthritis. Here, then, is an experiment in which acute polyarthritis is produced by injecting *sterile toxic* products from the gonococcus and, while it has not been proved as occurring in man, there is suggestive evidence at least that this mechanism may be important in some cases of arthritis in man, and in particular the cases with a local lesion and arthritis without demonstrable antibody formation until late in the disease.

In assessing any form of treatment of gonococcal arthritis, then, it is necessary to take these various factors and types of reaction into account. In a review of the treatment of 70 cases of gonococcal arthritis, Spink and Keefer[7c] recorded that the patients who have the worst outlook insofar as complete recovery from the arthritis is concerned are those falling into the second group. Those with the best outlook are the ones with pain and periarticular swelling, with very little effusion into the joints.

For the above reasons, we have divided our cases into three groups: 1, those with infected synovial fluid; 2, those with sterile synovial fluid; 3, those without effusion of fluid into the joints.

TABLE 1.—SUMMARY OF CASES.

Age.	Sex.	Duration of arthritis before drug (days).	Joints involved.	Duration of arthritis after drug (days).	Duration of infected synovial fluid (days).	Total amount of drug (gm.).	Duration of fever (days).	Reactions.	Hospital stay (days).	Local focus.	Results.
				Patients With Infected Synovial Fluid.							
49	♂	10	Right and left knee	12	4	46	14	None	31	*	R
22	♂	5	Right and left knee, right shoulder, right ankle.	63	6	82	30	None	84	S	R
34	♀	8	Metacarpal phalangeal, knees, hips, right wrist, left knee	21	3	12	21	Nausea, vomiting, anemia	42	S	R
40	♂	10	Right knee	10	3	82	3	None	16	*	R
41	♀	7	Both knees	28	7	12	9	Anemia	84	S	R
				Patients With Sterile Synovial Fluid.							
24	♂	6	Right knee	10	...	48	Afebrile	None	14	S	R
40	♂	7	Left knee	11	...	54	4	None. Recurrence of arthritis and fever following withdrawal of drug	..	*	R
52	♀	7	Right knee	10	...	21	13	Hemolytic anemia	25	*	R
30	♂	10	Right knee	14	...	22	16	None	..	S	R
				Patients Without Joint Effusions.							
30	♂	7	Right ankle, metacarpal phalangeal	4	...	78	14	Recurrence of arthritis on withdrawal	42	S	R
36	♀	3	Left knee, wrists, ankles, hands	4	...	76	16	Fever, rash, nausea	42	S	R
42	♂	2	Left ankle	3	...	64	5	Fever, rash	28	S	R
22	♀	4	Left elbow, right wrist, fingers right hand	1	...	20	2	None	5	†	I
32	♂	3	Knee, costo-sternal	6	...	78	4	None	35	N.S.	I

* Local focus undetermined.
R Recovered completely.
S Sterilized by sulphanilamide alone.
I Improved.
N.S. Not sterilized.
† Study incomplete.

Patients With Infected Synovial Fluid. From our previous experience[5] approximately 30% of patients with gonococcal arthritis have an infected synovial fluid at the time of our examination. Moreover, it is in this group of patients that the prognosis is less certain insofar as complete recovery of normal function of the joints is concerned, and they remain in the hospital the longer period of time. The average hospital stay in previously studied patients was 61 days.

In the present group, there were 5 patients with infected synovial fluid who were treated with sulphanilamide. The end results were surprisingly good in spite of the fact that the disease frequently remained active for a long period of time. They all recovered completely and without any permanent disability of the joints. The course of the disease varied from 16 days to 3 months and the main features have been summarized in Table 1.

There are certain features requiring comment. First of all, it was clear that sulphanilamide diffused into the synovial fluid in about the same concentration as that of the blood. Secondly, the synovial fluid was sterilized in from 3 to 7 days and in only 1 case were organisms found in the synovial fluid after sulphanilamide had been started. In this case, it is possible that the dosage was inadequate, since it was one of the first cases treated and quantitative studies of sulphanilamide in the synovial fluid were not made. When we have maintained the sulphanilamide control of synovial fluid above 5 mg. %, the fluid has been sterilized with regularity.

Sulphanilamide did not interfere with the appearance of antibodies, such as the complement-fixation reaction, so that it would appear that immune reactions were neither delayed nor prevented. This is significant since there is some evidence that the final destruction of the organism is due to the combined action of the chemical and the normal defense mechanism of the body. For example, too early withdrawal of the drug may be followed by a recurrence of the arthritis, fever, and an exacerbation of the urethritis. The temperature curve may not be strikingly altered for some days following its use.

It would appear from the study of these cases that, in spite of the sterilization of the synovial fluid within a relatively short period of time, the damage to the synovial membrane may require a long period for recovery. The end results, however, are most encouraging and certainly in our experience so far, at least, they are better than the other methods that we have employed in the past.

Figure 1 is a chart showing the course of events in a patient with an infected synovial fluid. In short, this 40-year-old man had been well until 2 weeks prior to admission to the hospital when he developed an acute respiratory infection which subsided within 4 days. Five days before admission to the hospital his right knee became stiff and painful and the next day it was greatly swollen. The only

point of significance in his past history was the occurrence of gonorrhea 20 years previously.

The examination showed nothing significant except the acute arthritis of the right knee, high fever, and leukocytosis of 12,300 per c.mm. No gonococci were recovered from the urethra or prostatic fluid. The figure shows that the synovial fluid was infected with gonococci when it was examined after the first tapping, and the gonococcal complement-fixation test on the blood was positive. Following sulphanilamide by mouth, the sulphanilamide content of the blood and synovial fluid increased so that at the time of the second tapping the synovial fluid was sterile and contained 5.7 mg. of sulphanilamide per 100 cc. Two days later the synovial fluid

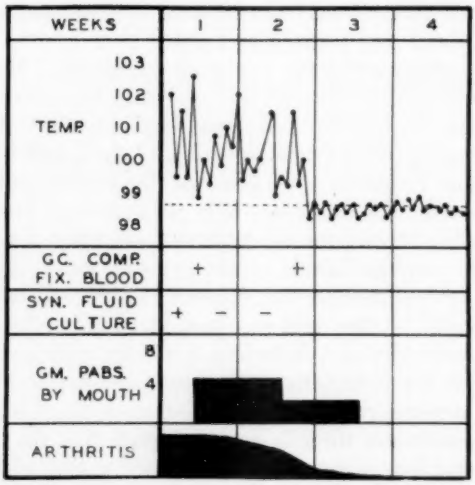

FIG. 1.—Patient with gonococcal arthritis with infected synovial fluid. Sterilization of synovial fluid following sulphanilamide when the concentration reached 5.7 mg. per 100 cc.

contained 7.7 mg. of sulphanilamide per 100 cc. The fever gradually subsided and the arthritis disappeared so that he was well, without any disability, at the end of 4 weeks.

This case shows that the synovial fluid can be sterilized before the temperature returns to normal but, following the sterilization, the arthritis begins to improve. Moreover, it illustrates the fact which has been stressed by us before[7c] that gonococcal infection of the joints may appear following a latent period after a primary infection, and it may be impossible to isolate the organisms from the genito-urinary tract and, secondly, these instances of arthritis not infrequently follow an attack of acute sore throat. Finally, there seems to be no question that the course of the arthritis was favorably influenced by sulphanilamide.

Patients With Sterile Effusions Into the Joints. All of the 4 patients of this group recovered without disability or deformities of the joints. The local lesion in the genito-urinary tract was sterilized in 3 of the cases on sulphanilamide alone. The duration of the fever was shortened, the effusion in the joints subsided rapidly, and the patients were improved in a shorter period of time than in similar cases treated with sulphanilamide. In a group of 22 similar patients treated without sulphanilamide, the average duration of their stay in the hospital was 53 days. In the 4 cases of the present group, it was 14, 21, 23 and 40 days, respectively, the average being 24 days.

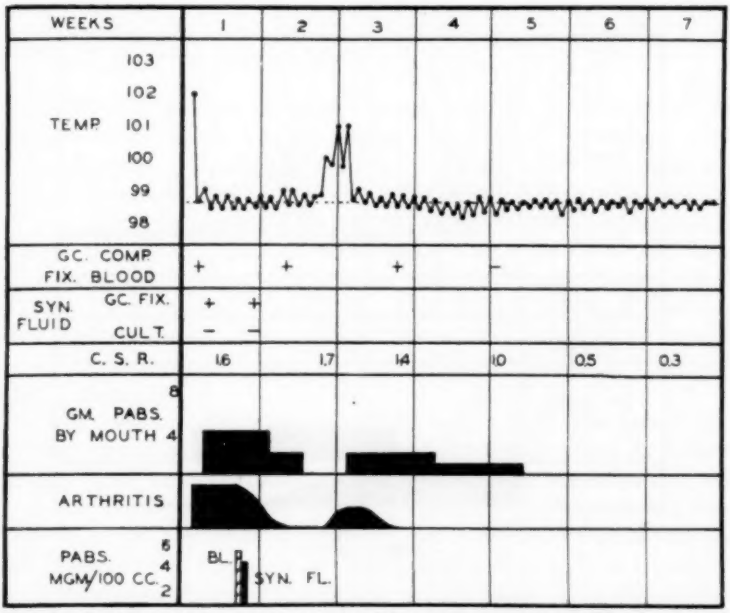

FIG. 2.—Patient with gonococcal arthritis, sterile synovial fluid, increased sedimentation rate, exacerbation of arthritis with withdrawal of fluid, positive gonococcal complement-fixation test.

One of the patients developed a hemolytic anemia from which she recovered following blood transfusion and a cessation of the drug. In another patient, there was a recurrence of fever and an exacerbation of the arthritis following its withdrawal (Fig. 2). In this patient, the symptoms subsided following the use of the drug once again. The story of this patient's illness was as follows:

Clinical History.—A man, aged 40, developed an acute arthritis of the left knee joint 7 days before admission to the hospital. The examination showed swelling, tenderness, and an effusion of fluid into the left knee joint, fever, and leukocytosis of 13,600 per c.mm. The gono-

coccal complement-fixation reaction was positive in both the blood and synovial fluid, but no organisms were recovered from the synovial fluid. The corrected sedimentation rate was increased. The synovial fluid contained 80,000 cells per c.mm., with 98% neutrophils. Following sulphanilamide, the cell count of the synovial fluid diminished, the temperature returned to normal, and the arthritis subsided. When sulphanilamide was withdrawn there was an exacerbation of the fever and arthritis. The sedimentation rate had not returned to the normal level when the sulphanilamide was discontinued. Following the use of the drug a second time, the arthritis again subsided and the cell count of the synovial fluid was reduced further. This case emphasized the importance of continuing the drug until all signs of the infection subside. This experience also suggests that another process aside from the action of sulphanilamide is responsible for complete recovery.

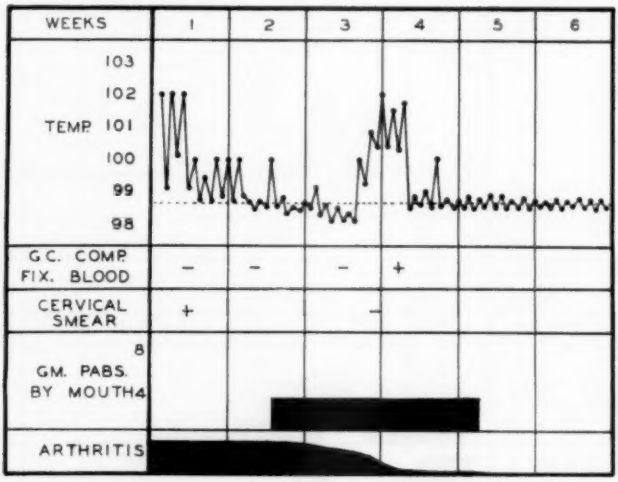

FIG. 3.—Gonococcal arthritis treated with sulphanilamide and followed by fever and skin eruption.

Patients Without Effusions Into the Joints. Five of the patients had gonococcal arthritis without sufficient effusion into the joints to enable us to obtain fluid for examination. In these, the diagnosis was made on a basis of the history, the presence of a local lesion, arthritis, and a positive complement-fixation test, together with the course of the disease. From previous experience[7e] we had found that 75% of such patients recover completely without any residual symptoms or signs referable to their joints. In the others, chronic changes followed, especially when the wrist joints were involved. The average hospital stay of this group was 50 days. Of the 5 patients in this group who were treated with sulphanilamide, the average duration of their hospital stay was 30 days.

An example of the course of the disease is shown in Figure 3.

A woman, aged 36, complained of pain and tenderness in the right shoulder and elbow and in the left knee. The examination showed the left knee to be swollen, red, and tender together with pain and tenderness in the right shoulder and elbow. She had fever and 10,700 leukocytes per c.mm., and the cervical smear was positive for gonococci and these organisms were grown from the exudate. The course of the illness is shown in the figure. During the first 10 days of observation her temperature fluctuated between normal and 102° F., and the arthritis persisted. The gonococcal complement-fixation test of the blood was negative. On the 12th day of the hospital admission sulphanilamide was started in daily amounts of 4 gm. On this treatment the arthritis subsided within 2 weeks and the local lesion was sterilized. On the 7th day after sulphanilamide she developed fever without an exacerbation of the arthritis which lasted 6 days and subsided. On the 18th day of treatment a maculopapular skin eruption appeared over the upper extremities. Following this, the drug was omitted. The gonococcal complement-fixation test became positive during the 4th week of observation. The skin eruption disappeared on the 2d day and she recovered completely.

In brief, this patient with gonococcal arthritis showed rapid and prompt improvement of the arthritis following treatment with sulphanilamide. The local focus was sterilized. Fever and a skin eruption appeared on the 7th and 18th days of treatment, respectively. The fever was self-limited in duration and disappeared in spite of the continuation of the drug. This case illustrates that sulphanilamide even in small doses may influence the course of arthritis favorably and sterilize the local focus. There is also evidence that the fever which follows the use of this drug may be self-limited in duration and, in some cases at least, disappear while the drug is continued.

Sulphanilamide in Synovial Fluid. Marshall, Emerson and Cutting[4] have shown that when sulphanilamide is given by mouth it is readily absorbed into the circulating blood and diffuses through all of the tissues with more or less evenness. We have found that it diffuses into the synovial fluid so that the concentration in the fluid is practically the same as in the blood, although in 1 case we found it to be as high as 3 times that of the blood. This observation is helpful in understanding the reason that the synovial fluid may be sterilized with rapidity following the administration of the drug. That is to say, it appears that synovial fluid containing sulphanilamide will fail to support the growth of gonococci. In other work, we[1] have found that when the concentration of sulphanilamide is above 5 mg. % gonococci will not grow. Whether or not they are killed or die seems to depend somewhat upon the type of culture medium. It is perhaps well to recall that when the culture medium is changed so that organisms cannot reproduce, they frequently die, so that it is not possible to draw a sharp line between a bacteriostatic and a bactericidal effect *in vitro*. Table 2 shows the values of sulphanilamide in the blood and synovial fluid at the same time in 4 different patients.

TABLE 2.—COMPARISON OF SULPHANILAMIDE LEVEL IN THE BLOOD AND SYNOVIAL FLUID.

Patient.	Blood sulphanilamide, mg. per 100 cc.	Synovial fluid sulphanilamide, mg. per 100 cc.
1	5.9	5.7
	8.2	7.7
2	5.1	4.1
	2.3	1.9
3	5.8	6.1
4	6.2	18.8

From previous experience with infected synovial fluids, we have been unable to sterilize the fluid as quickly by any other means, so that it would seem advisable to give the drug so that the concentration in the blood and synovial fluid is at least 5 mg. per 100 cc.

Cellular Reaction in Synovial Fluid Following Sulphanilamide. It has been noted frequently by us[5] that the total cell count is often higher in infected fluid than it is in sterile specimens. Moreover, as the patients improve, the total cell count diminishes and the neutrophils become less numerous. McEwen[3] has found that following the aspiration of the knee joint there may be a temporary increase in the total number of cells in the synovial fluid; later as improvement occurs the number of cells decline.

When the knee joints of our patients were aspirated repeatedly and the cell counts followed before and after sulphanilamide, it was found that following the first aspiration there frequently was an increase in the total cell count but, as the fluid became sterile, the cells diminished rapidly in number; or, if it were sterile at the beginning, the number of cells per cubic millimeter diminished with improvement. The results in 9 cases are shown in Table 3.

These data tend to show that the intensity of the inflammatory reaction is reduced following sulphanilamide, and this may be taken as a favorable sign of improvement.

The Effect of Sulphanilamide on the Local Infection in the Genito-urinary Tract. It is now known that following sulphanilamide by mouth, profound changes may occur in some cases of gonococcal urethritis. In about one-half the cases the clinical signs of infection disappear and the local focus is sterilized. In other cases, the clinical signs of the infection disappear but the organisms remain in the local focus in spite of the use of sulphanilamide. These latter cases serve to emphasize the importance of the local body defense mechanism in the final destruction of organisms in most if not in all cases. Moreover, it is of the highest importance that these cases be recognized since these latent infections may be the cause of spreading the disease to others.

In the 14 cases of arthritis studied, the primary focus was determined in 11. In 2 of the remaining 3 cases the organisms were isolated from the synovial fluid and, in the final case, the clinical course

and the serological test justified the diagnosis. Of the 11 cases, in which the primary focus was determined by culture of urethral or cervical exudates, 8 were sterilized before they left the hospital

TABLE 3.—SUMMARY OF SYNOVIAL FLUID EXAMINATIONS BEFORE AND AFTER SULPHANILAMIDE.

Case.		Total cell count.	Culture.	Gonococcal complement-fixation test.	Sulphanilamide, mg. per 100 cc.	
					Blood.	Synovial fluid.
1	Before sulphanilamide	13,700	+	+	−	−
	After sulphanilamide					
	4th day	21,600	−	+	5.9	5.7
	7th day	16,000	−	+	8.2	7.7
2	Before sulphanilamide	80,000	−	+	−	−
	After sulphanilamide					
	2d day	51,000	−	+	5.1	4.1
	15th day	19,800	−	+	2.3	1.9
3	Before sulphanilamide	10,000	−	±	−	−
	After sulphanilamide					
	3d day	3,350	−	+	5.8	6.1
4	Before sulphanilamide	20,000	−	−	−	−
	After sulphanilamide					
	3d day	57,000	−	+	6.2	18.8
5	Before sulphanilamide	37,500	+	−		
	After sulphanilamide					
	3d day	45,000	−	−		
	5th day	26,000	−	±		
	8th day	11,500	−	+		
6	Before sulphanilamide	23,000	+	−		
	After sulphanilamide					
	4th day	37,500	−	+		
	6th day	25,350	−	+		
	8th day	20,000	−	+		
7	Before sulphanilamide	24,000	+	−		
	After sulphanilamide					
	10th day	20,000	−	+		
8	Before sulphanilamide	57,500	−	−		
	After sulphanilamide					
	3d day	57,000	−	−		
	7th day	80,000	+	−		
	9th day	85,000	+	−		
	11th day	85,000	−	−		
	15th day	70,000	−	−		
	17th day	60,000	−	−		
	19th day	55,000	−	−		
	25th day	50,000	−	−		
	32d day	50,000	−	−		
	39th day	40,000	−	−		
	51st day	15,000	−	−		
9	Before sulphanilamide	9,000	−	+		
	After sulphanilamide					
	5th day	11,000	−	+		

by the use of sulphanilamide alone. In 2 it was not possible to sterilize the local focus and, in 1, the patient left the hospital before the studies could be completed. These observations serve to indicate that it has not been possible in all cases to sterilize local foci of infection in the genito-urinary tract with sulphanilamide alone. This would suggest that the final destruction of the organism, in some cases at least, is due to the defense mechanism of the body.

Recurrence of Arthritis or Urethritis Following Withdrawal of the Drug. One of the conspicuous features in several of the cases was the recurrence of the arthritis following the withdrawal of the drug. In 1 patient this occurred on 2 occasions, and in another it was observed once.

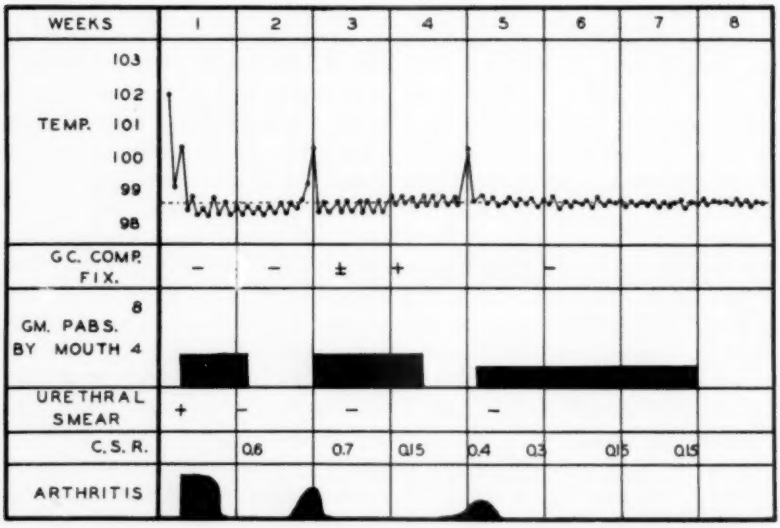

FIG. 4.—Patient with gonococcal arthritis treated with sulphanilamide. The local lesion was sterilized in 5 days. Two exacerbations of the arthritis with fever, following withdrawal of drug. Gonococcal complement-fixation test positive 16th day of observation. Sedimentation rate increased with increase in joint symptoms.

The course of events is shown for one of these cases in Figure 4. It can be seen that the temperature had returned to normal, the urethral exudate no longer contained gonococci, and the symptoms of arthritis had disappeared. The complement-fixation reaction, however, was negative and the corrected sedimentation rate was still elevated when the drug was withdrawn the first time. Five days after the drug was withdrawn, fever returned and there was an exacerbation of the arthritis. When the drug was readministered the arthritis and fever again disappeared. Ten days later, when the complement-fixation reaction was positive and the corrected sedimentation rate was normal, the drug was again withdrawn. Within 4 days there was another exacerbation of the fever and arthritis, and the sedimentation rate increased once again. All of these features disappeared following sulphanilamide.

A somewhat similar case is shown in Figure 2. Here there was fever and an exacerbation of the arthritis within 3 days after the withdrawal of the drug. It will be noted that the corrected sedimentation rate was still elevated above normal at the time of the examination.

In other cases, the continuation of the fever during the administration of the drug, even when the local infection of the urethra seems to be improving, may be due to an active infection in the joints which has not been adequately controlled. Figure 5 is an example of such a case and, since it illustrates several points, it requires comment.

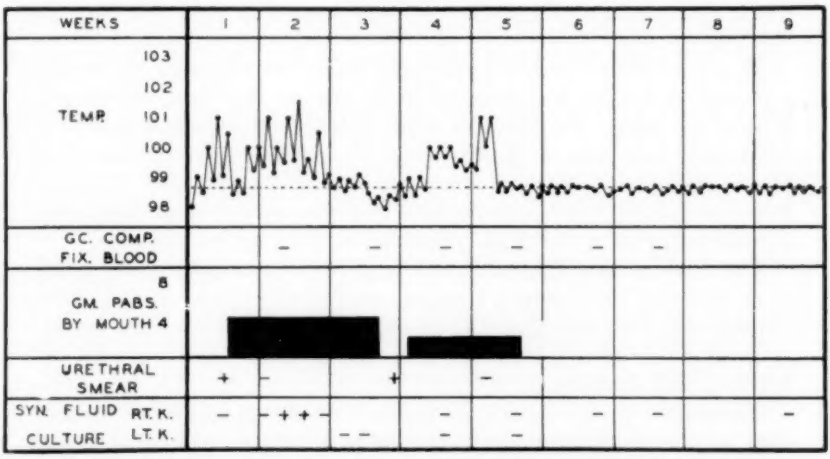

FIG. 5.—Gonococcal arthritis with recurrent effusions of fluid into the joints, a poor antibody response and an exacerbation of urethritis following the withdrawal of sulphanilamide.

A young colored boy with acute gonococcal urethritis and arthritis was given sulphanilamide by mouth for 2 weeks. The fever continued during this period although it tended to approach normal. During this time the urethral discharge became scanty and gonococci were not recovered from it. The synovial fluid from the right knee, which was at first sterile, became infected and the left knee became involved. When the drug was discontinued for 3 days, the urethral discharge again contained organisms and then disappeared when the drug was again started. When the drug was commenced a second time, there was an exacerbation of fever which was difficult to interpret. However, the effusion into the joints continued to recur. One important feature of the case was the failure of the patient to develop an immune response to the infection insofar as complement fixation antibodies were concerned.

This case served to emphasize that sterile fluid may continue to reaccumulate in the joints following sulphanilamide, that there may be an exacerbation of the urethritis following its withdrawal, and that the synovial fluid may contain gonococci during the time of its administration. Unfortunately, we do not have exact informa-

tion concerning the amount of sulphanilamide in the synovial fluid, but it is impressive that this patient never developed a positive complement-fixation reaction, suggesting at least that this patient had a poor or, at best, a slow immune response to the infection, and that this poor response on the part of the patient was responsible for the prolonged course of the disease.

Side Effects. Four of the 14 patients showed the side effects of the drug. One patient developed hemolytic anemia, 2 showed febrile reactions with a rash, and 1 had fever without any other signs of intoxication. Practically all of the patients were cyanotic; 1 had nausea, vomiting, and diarrhea; and all of them were somewhat depressed and complained of weakness while they were taking the drug.

The patient who developed the hemolytic anemia recovered promptly following blood transfusion, forcing of fluids, and cessation of the drug. In the individuals who developed fever and skin eruptions there was a prompt recovery following the withdrawal of the chemical. There is some evidence that leads one to believe that the febrile reactions are self-limited in extent since they disappear even when the drug is continued after fever reappears.

The various side effects of the drug have been amply discussed elsewhere and they need not be repeated at this time. It is well to emphasize, however, that the most alarming reactions are hemolytic anemia, agranulocytosis, and the febrile reactions with or without skin eruptions.

Comment. From the results in the 14 cases it seems fair to say that sulphanilamide in adequate dosage affects the course of gonococcal arthritis in a striking manner. In order to accomplish the best results it is necessary to increase the concentration of the drug to at least 5 mg. % or higher in the circulating blood and synovial fluid. This can usually be done by giving 4 or 5 grams (60–75 grains) a day in divided doses. Since there is some variation from one patient to another in the rapidity with which they absorb and maintain the sulphanilamide level in their blood, it is necessary to check the blood level every 2 days during treatment. In the patients with sterile synovial fluid there is evidence that the cell count diminishes and the fluid reaccumulates less rapidly after its administration, and the duration of the illness is shortened. When this level is reached, the growth of organisms in the synovial fluid is inhibited and it becomes sterile. Moreover, there is often a profound effect on the local focus in the genito-urinary tract so that it is sterilized much sooner than frequently happens during the natural history of the disease.

The studies of the action of sulphanilamide *in vitro* on the gonococcus would indicate that it inhibits the growth of the organism in whole blood or in other media and, when the concentration is

adequate, organisms fail to survive. When it is given to patients with gonococcal infection it would appear to exert a profound inhibitory effect on the growth of the organism but it does not cause sterilization of foci of infection in all cases. Moreover, when the drug is withdrawn, there is often a recurrence or exacerbation of the signs of infection. These observations suggest that the normal defense mechanism of the body plays a marked rôle in the final destruction of the organism in the host. For the optimum results, then, one should have a sufficient concentration of the drug in contact with the organisms and a defense mechanism that is capable of destroying organisms.

From the results that we have observed in this small group of cases, it is fair to say that the results are encouraging and that all patients with gonococcal arthritis should be treated intensively with the drug.

Summary and Conclusions. From a study of 14 patients with gonococcal arthritis who were treated with sulphanilamide the following facts emerged.

1. Sulphanilamide has a striking effect on the growth of the gonococcus *in vitro* and *in vivo*. To produce the optimum effect it is necessary to have a concentration of 5 or more mg. per 100 cc. in the blood.

2. The drug diffuses into the synovial fluid and is present in approximately the same concentration as it exists in the blood.

3. The infected synovial fluid is sterilized within several days after the drug is administered, provided the concentration is adequate.

4. Recurrences of the arthritis, fever, and the urethritis may follow the withdrawal of the drug. It is well to continue its use until the sedimentation rate is normal and, if the complement-fixation reaction has been negative, it should be continued until it is positive.

5. The most striking results were obtained in patients with infected synovial fluid.

6. There is some evidence that the body defense mechanism is of importance in ridding the body of organisms.

7. The side effects are of sufficient frequency so that all patients who are receiving the drug should be followed with care.

REFERENCES.

(1.) **Keefer, C. S.**, and **Rantz, L. A.**: Am. J. Syph., Gon., and Ven. Dis., **22**, 679, 1938. In press. (2.) **Keefer, C. S.**, and **Spink, W. W.**: (*a*) J. Clin. Invest., **17**, 23, 1938; (*b*) Am. J. Syph., Gon., and Ven. Dis., **21**, 241, 1937. (3.) **McEwen, C.**: J. Clin. Invest., **14**, 190, 1935. (4.) **Marshall, E. K., Emerson, K.**, and **Cutting, W. C.**: J. Am. Med. Assn., **108**, 953, 1937. (5.) **Myers, W. K., Keefer, C. S.**, and **Holmes, W. F., Jr.**: J. Clin. Invest., **13**, 767, 1934. (See Ref. 3.) (6.) **Ralston, J. D.**: Personal communication. (7.) **Spink, W. W.**, and **Keefer, C. S.**: (*a*) J. Clin. Invest., **16**, 169, 1937; (*b*) Ibid., p. 177; (*c*) J. Am. Med. Assn., **109**, 325, 1937; (*d*) J. Clin. Invest., **17**, 17, 1938; (*e*) New England J. Med., **218**, 453, 1938.

CLINICAL STUDIES IN CIRCULATORY ADJUSTMENTS.

V. Clinical Evaluation of Cardiodynamic Studies.*

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In evaluating the condition of the circulation, it must be stressed that a single look on the clinical state of the patient often tells more than many painstaking tests devised to measure the efficiency of the circulatory apparatus. This is largely because the look is "correlative"—the patient is seen as a whole. If a quantitative measure of the circulation is desired, however, the circulatory apparatus must be divided into several components or aspects—the volume circulated, the speed of circulation, the pressure, and so on, divisions that depend arbitrarily on the scientific methods available for quantitative assay of the circulation. Thus the important components that can be measured without too great difficulty are circulating blood volume, cardiac output, circulation time, venous pressure, blood pressure and cardiac rate. In order to integrate and correlate the different components of the circulation to give a better evaluation in any particular patient a schema for showing the relationship between the important factors maintaining circulatory equilibrium has been devised (Fig. 1).

Reference to the figure shows that the total amount of blood in the body available for circulation is of two kinds, one actively circulating, and the other slowly circulating, stored blood—the important storage organs or blood depots being the liver, spleen, lungs, skin, muscles and splanchnics. The total volume of actively circulating blood makes one round of the circulation in a *revolution period*. The length of the revolution period varies directly with the *volume of blood* that is circulating and inversely with the *rate of the heart* and the amount of blood pumped out by the heart with each stroke (*stroke volume*). Perhaps the most important factor influencing the rate of the heart and thus indirectly the size of the cardiac stroke is the volume of blood returned to the right auricle, the venous return, which depends directly on the venous pressure.

* This study was made possible by the fund generously established for this purpose by Mr. Henry Dazian.

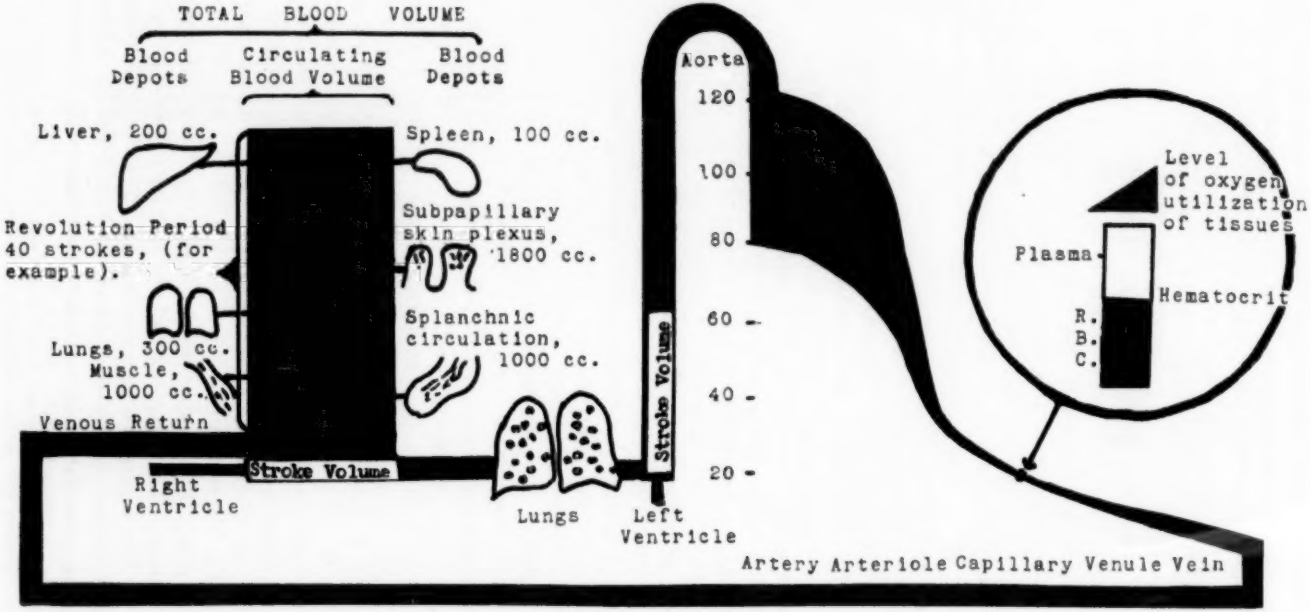

FIG. 1.—Schema showing relationship of factors maintaining circulatory equilibrium.

The schema further represents the blood as circulating through the lungs, where it becomes oxygenated, and is returned to the left ventricle, the important pumping station that must impress the proper "head of pressure" on the blood pumped into the systemic circulation. This "head of pressure" falls slowly through the arterial branches, and very rapidly through the arterioles and capillaries before it reaches the tissues. From the tissues the blood collects in venules and larger veins to be returned to the right heart at a rate determined by the venous pressure.

It is unfortunately impossible to measure with exactness the revolution period (the average time it takes for the whole body of actively circulating blood to make the round of the circulation), since there are so many varied pathways the blood may take, and since there is such great variation of the speed of different parts of the blood in the same blood-vessels, *i. e.*, faster in the central stream, slower on the sides. The closest approach to the desideratum possible with our present-day methods is to measure the time for the *fastest moving* particles to traverse a definite circuit. This is called *circulation time*, and is designated by the names of the two points which mark the beginning and end of the circuit—vein to lung circulation time, and so on. Figure 2 was drawn to show (among other things) the different circuits used today in measuring the speed of circulation. A more detailed consideration will be taken up in the section dealing with circulation time.

We now turn to a consideration of the methods used to determine these different components of the circulation so that we can finally attempt a clinical evaluation of their usefulness.

Blood Volume. It has been shown experimentally (Barcroft[1] and others) that the total amount of blood in the body does not circulate with the same speed through all the organs. There are some in which the blood circulates rapidly, actively, while in others, such as the spleen and liver, the circulation is very much slower, making of these latter organs a sort of reservoir where the blood is stored rather than actively circulated. *These organs which are able to store blood and release it to the circulation when needed without detriment to the organ or any other part of the body are called blood depots.** The exact mechanism by which the blood is stored and later given up to the active circulation concerns us in that it helps clarify the nature of the blood depots.

In the spleen the blood appears to be *shunted* into the numerous venous sinuses. The hoarding and discharging of blood is regulated largely by the vegetative nervous system (Rein[12]). Stimulation of the vagus system causes the spleen to hoard blood, while with sympathetic stimulation (as with increase of adrenalin in the blood),

* Figure 1 shows the important blood depots and the amount of blood they are capable of releasing into active circulation (estimated, not measured). Note that the amount of stored blood is almost equal to the circulating blood volume.

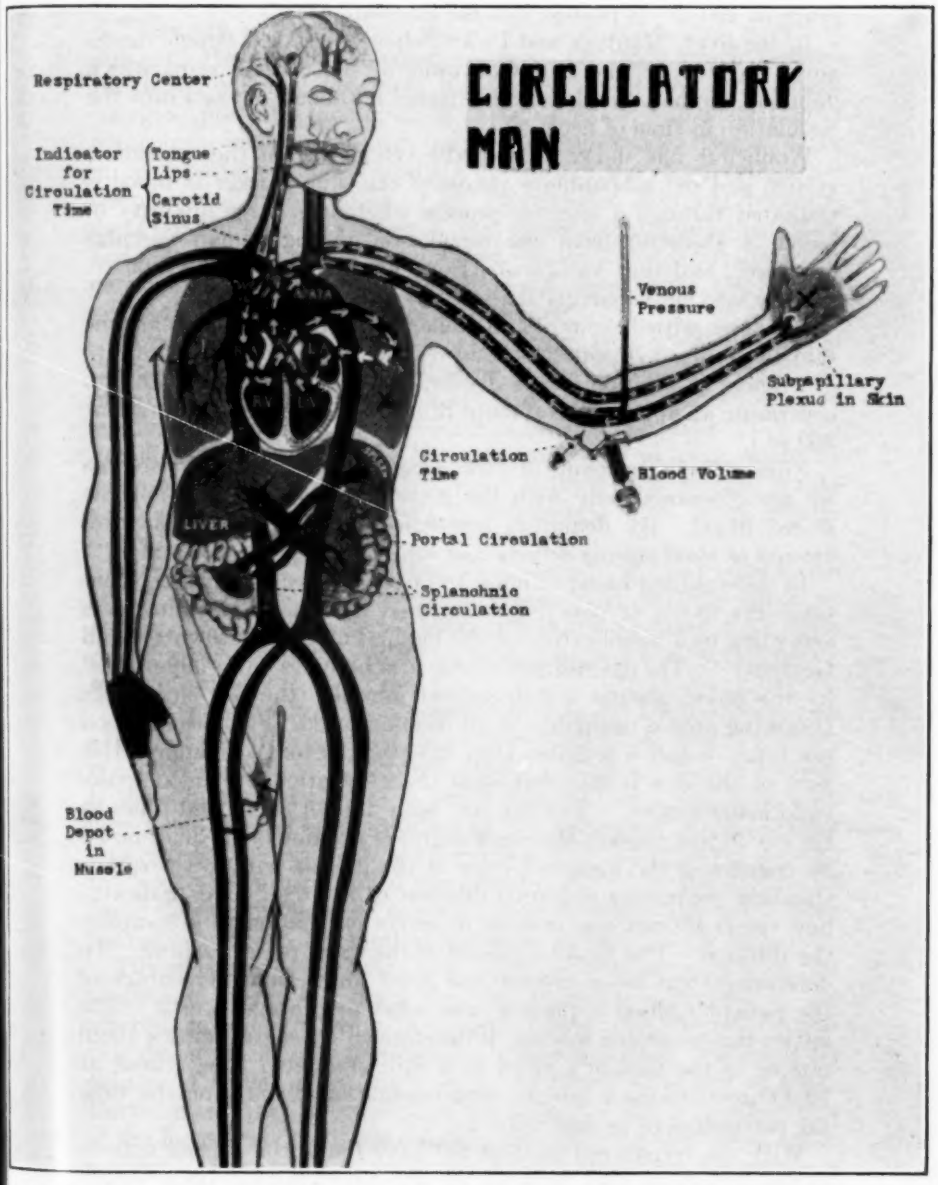

FIG. 2.—Circulatory man—a diagrammatic representation of the cardiovascular apparatus and blood depots. (See text for fuller discussion.)

the spleen contracts and the greater part of the stored blood (as much as 100 cc.) is pushed into the circulation.

In the liver, Mautner and Pick[11] believe there is a *throttle* mechanism exerted by the muscular walls of the central veins which dams up the blood and then discharges it (about 200 cc.) into the circulation in time of need.

Wollheim[17] has shown that in the venous bed of the splanchnic system and the subpapillary plexus of the skin, storage of blood is mediated through a *blockage* process whereby a large quantity of blood is absorbed from the circulation through small vascular apertures; and that vasoconstriction empties as much as 1800 cc. quickly into active circulation.

We agree with Hochrein and Keller,[7] that the lungs may also be said to be blood depots which, by change in their volume (due to differences in position of the diaphragm and the ribs), are able to contribute an appreciable amount of blood to the circulation (about 300 cc.).

From the clinical point of view, when we speak of blood volume we are concerned only with the actively circulating and not the stored blood. By definition *circulation blood volume is the total amount of blood moving actively and rapidly through the circulation.*

In determining blood volume 10 cc. of an easily diffusible, nontoxic dye (0.6% trypan red) is injected into one antecubital vein according to a modification of the method of Keith, Rowntree and Geraghty.[8] The dye diffuses readily and becomes uniformly diluted by the blood plasma within several minutes (the red blood cells absorbing only a negligibly small fraction of it). Samples of blood are taken 3 and 6 minutes after injection, before any appreciable part of the dye is removed from the circulation by the reticuloendothelial system. The dye has been diluted about 500 times in the circulating plasma, the exact degree of dilution being determined by comparing the imparted color of the plasma withdrawn with a standard containing a known dilution of the dye. This indicates how much plasma was present in active circulation to accomplish the dilution. The figure obtained is the total *plasma volume.* To determine total blood volume one must know what percentage of the patient's blood is plasma, and what percentage is cells. The latter, the *hematocrit reading*, is determined by centrifuging a small sample of the patient's blood in a thin graduated tube ½ hour at 10,000 revolutions a minute, and reading off directly on the tube the percentage of packed cells.

With the trypan red method we[4] have found the plasma volume in the normal to vary between 36 and 49 cc. per kg. body weight (average 40.5), and the total circulating blood volume from 66 to 90 cc. per kg. (av., 78.4). The hematocrit varied from 36.5 to 50.5% (av., 43.8%). The total plasma volume averaged 2780 cc.; the

total circulating blood volume, 5386; the average circulating blood volume per square meter of surface area was 3037 cc.

There are certain physiologic factors that have been shown to influence the circulating blood volume. Of those which increase the blood volume one must mention exercise, low atmospheric (oxygen) pressure, inhalation of carbon dioxide, administration of epinephrin, caffeine, pituitrin or thyroid substance. Some of the more important factors causing a decrease of the blood volume are sleep, postoperative shock, high atmospheric (oxygen) pressure, diets poor in salts and nitrogen, and drugs like digitalis, histamine and morphine. The changes in blood volume which occur in various pathologic conditions will be discussed later with the clinical evaluation of the usefulness of this method.

Cardiac Output. Perhaps more important than the knowledge of the total amount of blood available in the organism is the determination of how efficient the heart is as a *pump* keeping the blood circulating, *i. e.*, how fast the heart is beating, and how much it is expelling with each beat. The first is arrived at very easily by listening to and counting the heart sounds—the second, stroke volume (and cardiac output) is determined with much greater difficulty.

The cardiac output is defined as *the amount of blood pumped out by the ventricle into the periphery, expressed in terms of liters per minute. The amount ejected with each systole is called the cardiac stroke, systolic output, or stroke volume, and is evidently the cardiac output divided by the heart rate.*

The Grollman method in general use now for the determination of cardiac output is based on the principle that blood flowing through the lungs enters into equilibrium with a foreign gas that is inhaled. If the solubility of the gas in blood is known, and one determines how much gas has been absorbed by the pulmonary blood during a unit of time, one can calculate the amount of blood flowing through the lungs that accomplished this absorption. Since the amount of blood flowing through the lungs is the same as the amount flowing through the heart, the method measures cardiac output indirectly.

The efficiency of the heart as a pump depends not only upon the amount of blood but upon the concentration of oxygen in the arterial, as compared with the venous blood. An efficient circulation maintains a high *arteriovenous oxygen difference*, defined as *the number of cc. of oxygen given up to the tissues by a liter of blood.* Furthermore, the oxygenation of the tissues is not only a function of the lungs and blood, but depends also upon the individual tissue activity. *The ability to utilize the oxygen brought to the tissues* is called the *oxygen utilization*, and is calculated as the arteriovenous oxygen difference divided by the total oxygen content of the arterial blood.

The Grollman method of determining cardiac output using acetylene as the foreign gas need not be detailed here; his monograph covers this subject adequately.[5] In essence the method requires the breathing from a bag of a gas mixture containing about 25% acetylene until it comes into equilibrium with the pulmonary blood (about 6 cycles of inspiration and expiration), then taking a sample of the mixture in the lung-bag system. After 3 more cycles another sample of alveolar air is collected. When the oxygen, carbon dioxide and acetylene in the 2 samples are analyzed in a Haldane apparatus, sufficient data are obtained for cardiac output determination, if the basal metabolism is known.

Using a modification of the Grollman method in 50 cases, we[2c] have found the cardiac output in normals to vary between 3.24 and 4.38, the average being 3.96 liters per minute. The stroke volume varied between 42 and 63 cc. with an average of 54 cc. If a less variable and more scientifically correct figure is desired, the results should be expressed in relationship to the surface area. This figure, the *cardiac index*, is the *cardiac output divided by body surface area*, and in the normal varied from 2 to 2.43, the average being 2.23 liters. The arteriovenous oxygen difference ranged from 49 to 63 cc. and averaged about 53 cc.

It is to be noted that cardiac output in its intimate relationship to oxygenation of the tissues is so fundamental a function of the body that it can be calculated for the normal individual and found to coincide with the measured values as closely as the basal metabolism can be calculated for the normal. The findings in abnormal cases will be discussed later in the second part of this article.

Venous Pressure. An important factor in the circulation is the pressure of the blood returning to the heart. By the Bainbridge reflex discussed before, an increase in venous pressure causes an increase in cardiac rate and is therefore important in regulating cardiac output. *The venous pressure may be defined as the residue of pressure in the venous side after the resistance in the arteries, arterioles, capillaries and venules has been overcome.* There are many factors affecting the venous pressure aside from the efficiency of the heart in maintaining the vis-a-tergo. Extracardiac factors are found all along the course of the veins—the contraction of the muscles in which the veins are embedded, the intra-abdominal pressure, changes in intrapulmonary pressure due to inspiration and expiration, the competency of the venous valves, and so on. There are also localized conditions, such as mediastinal tumor or aneurysm which cause an increase in venous pressure (usually unilateral).

A reliable way of determining venous pressure is the direct method of Taylor, Thomas and Schleiter,[16] which simply calls for venipuncture of the antecubital vein, the arm being held at the mid-level of the right auricle and the needle connected to an L-shaped hollow tube. The level that the blood rises to indicates the venous pressure

directly in centimeters. In our normal cases[3] the venous pressure figures ranged between 4.2 and 7.8 cm. (av., 5.36 cm.). The importance of increased venous pressure clinically will be discussed later.

Circulation Time. Aside from knowing the amount of blood available for circulation and the amount pumped out by the heart in a unit of time, one would like to know the velocity of blood flow. The speed of flow is evidently very variable, the mean velocity in the aorta being probably close to 50 cm. per second, in the capillaries possibly only 0.5 mm. per second, and again in the large veins about 15 cm. per second. There are so many available avenues of flow for the blood that it is impossible to test with exactness the total mean velocity. However, if comparative figures only are desired, one could determine the speed of blood flow in a characteristic circuit. A convenient one that is most often chosen for this is the vein-to-head circuit (Fig. 2). In the majority of our cases we have used the cyanide method proposed by Robb and Weiss[13] for the determination of pulmonary circulation time. Sodium cyanide solution, 0.25 cc. of 3%, is injected into the antecubital vein. As Figure 2 shows, the cyanide is carried through the right heart and lungs back to the left heart to be finally ejected into the systemic circulation. The first appreciable quantity of cyanide reaching the carotid sinus sets up a reflex respiratory stimulation which causes the patient to take a few deep breaths. The time interval between injection and the first signs of respiratory stimulation marks *the time it took for the fastest moving foreign particle to traverse the circulation between the two chosen points, peripheral vein and neck.* This is the circulation time between these two points, and is usually designated as *pulmonary circulation time.*

It depends upon the substance used as to what the circulation time will be. Thus, if instead of cyanide, 0.3 cc. of ether is injected into the antecubital vein, as suggested by Hitzig,[6] it will go through the right heart and into the lungs where the odor of ether would be detected as soon as this highly volatile substance reached the pulmonary arterioles (and capillaries). The circulation time determined in this manner is shorter, since it measures the speed through the right heart circuit only. The speed through the left heart circuit can be obtained by subtracting the vein-lung ether time from the vein-head cyanide time (Fig. 2).

The average circulation time from arm to head by the cyanide method in our normal cases[4] is 12 to 21 seconds (av., 16 seconds). The arm-to-lung time (right heart circuit) is 3.5 to 8 seconds (av., 6 seconds).[6] The circulation time for the left heart circuit is therefore 16 minus 6, or about 10 seconds average. The clinical significance of variations from the normal figures will be discussed later.

Clinical Evaluation. In evaluating the clinical usefulness of the cardiodynamic studies outlined above, one must draw a distinction between the use made of the fundamental experimental studies in

laying the physiologic basis for our concept of certain clinical diseases, especially cardiac, and the present-day application of the methods in the study of a patient. Historically we owe a great debt to these studies in helping us explain the essential disturbances in a great many clinical disorders, even if it is no longer important to reaffirm these relationships when confronted with a similar case in our clinical practice.

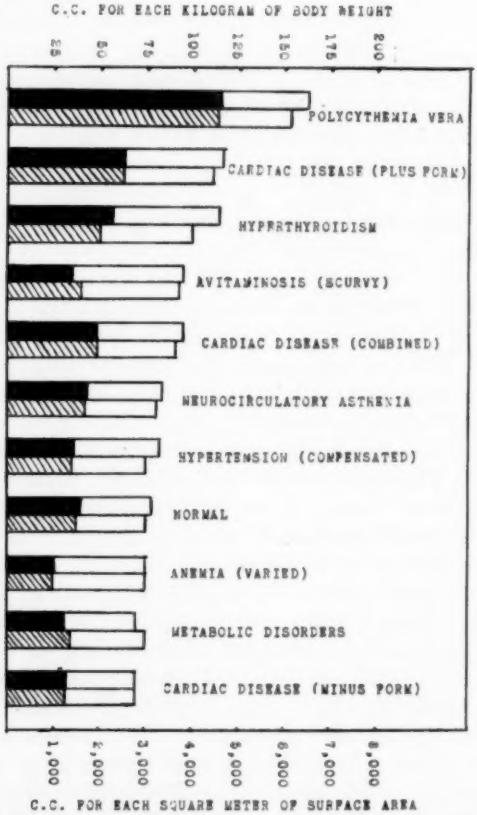

FIG. 3.—The circulating blood volume in varied conditions is represented by the total height of the columns; the solid column indicating the blood volume for each kilogram of body weight, and the cross-hatched the blood volume for each square meter of surface area. The clear area of each column represents the plasma volume.

In hypertension, for example, the marked elevation in blood pressure had led us to expect marked changes in the other cardio-dynamic factors which help maintain the circulatory equilibrium. But the actual measurements of these factors (which our work corroborates)* show that aside from a very slight increase in oxygen

* Demonstrated by the authors in an exhibit on the Cardio-dynamic Factors in Hypertension at the Scientific Fortnight, the Academy of Medicine, November 1 to 12, 1937.

consumption and a concomitantly small increase in cardiac output (an average of 4.46 liters where the normal is 3.96), there is no significant change in the circulation. Before decompensation sets in, hypertensives have normal blood volumes, venous pressures, circulation times and heart rates (Figs. 3, 4 and Table 2). There must evidently be some mechanism of compensatory dilatation of blood-vessels to negate the effect of increased peripheral resistance

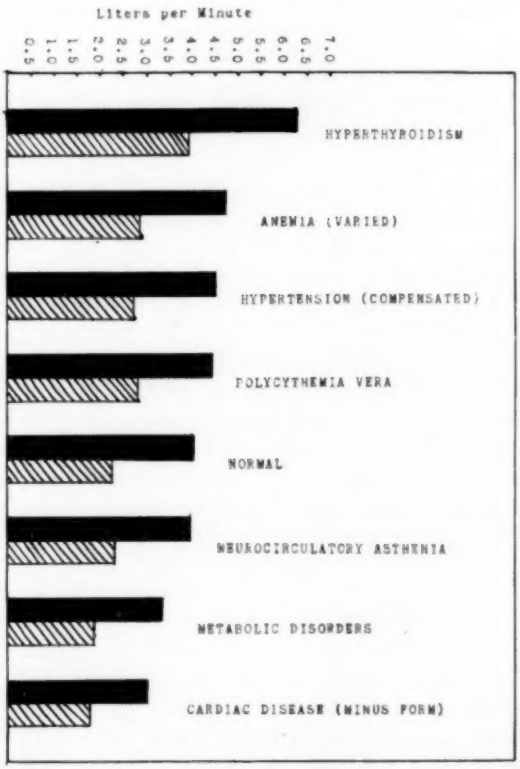

FIG. 4.—The solid columns indicate cardiac output in liters per minute. The cross-hatched columns represent cardiac output per square meter of body surface (cardiac index). The figure shows a more constant value for cardiac index, as compared to cardiac output.

on the circulation (Table 1, a summary of the cardiodynamic findings in the varied hypertensive states).

In these cases of essential hypertension, the decompensation which first sets in is typically that of left ventricular failure. The disturbance manifests itself mainly by pulmonary congestion because of the impeded pulmonary blood flow, the rigidity of the lungs and the diminution in the capacity of the alveolar spaces; clinically it

shows itself as decreased vital capacity, dyspnea, cyanosis and orthopnea. At first, while the failure is limited to the left side, there is no disturbance in the cardiodynamic factors, except for the circulation time. Due to the retardation of flow through the pulmonary circuit one will find a prolongation of the pulmonary circulation time (arm-to-head), while the time of circulation from the arm to the lung will still be normal.

TABLE 1.—TYPICAL CASES ILLUSTRATING THE CARDIODYNAMICS IN VARIED STATES OF HYPERTENSION.

Clinical case.	Sex.	Body weight, kg.	Body surf., sq. m.	Blood pressure, mm. Hg.		Plasma volume.		Blood volume.		Hematocrit, %	Arteriovenous oxygen difference.	Minute volume, liters.	Cardiac index.	Cardiac stroke, cc.	Circulation time (cyanide), sec.	Venous pressure, cm.
				Systolic.	Diastolic.	Cc. per kg. body weight.	Cc. per sq. m. body surf.	Cc. per kg. body weight.	Cc. per sq. m. body surface.							
Normal	M	57.2	1.62	110	70	42.3	1499	84.9	3000	45	62	3.24	2.0	42	17	4
Essential hyperten. plus decompensation	F	55.8	1.44	250	140	55.8	1922	148.2	5093	57	*	*	*	*	21	34
Hypert. coronary minus decompensation	M	82.0	1.89	200	130	33.0	1370	54.8	2715	36	60	3.28	1.7	46	..	5
Hypert. obesity, metabolic	M	92.7	1.97	210	75	35.3	1671	59.9	2819	37	84	3.36	1.7	42	13	8
Polycythemia vera	M	70.4	1.70	150	90	33.4	1252	132.9	4970	68	67	3.60	2.1	45	12	4
Hypert., compensated	M	71.8	1.71	205	120	36.0	1505	69.7	2929	44	50	4.60	2.7	47	16	7
Hyperthyroidism active	M	52.0	1.53	150	85	60.0	2032	129.0	4407	48	55	5.30	3.5	43	10	8

* Not determined because of orthopnea.

TABLE 2.—AVERAGE CARDIODYNAMIC VALUES IN VARIOUS CLINICAL CONDITIONS, SHOWING BLOOD PRESSURE, CIRCULATING BLOOD VOLUME, CARDIAC OUTPUT, VENOUS PRESSURE AND PULMONARY CIRCULATION TIME.

Clinical case.	Number studied.	Body weight, kg.	Body surface, sq. m.	Blood pressure, mm. Hg.		Blood volume.				Hematocrit, %.	Cardiac output.							Pulmonary circulation time (cyanide), sec.
				Systolic.	Diastolic.	Cc. plasma vol. per kg. wt.	Cc. plasma vol. per sq. m. surf.	Cc. total blood vol. per kg. wt.	Cc. total blood vol. per sq. m. surf.		Oxygen consumption per min.	Pulse.	Arteriovenous oxygen difference, cc.	Minute volume, liters.	Cardiac index.	Cardiac stroke, cc.	Venous pressure, cm.	
Normal	10	68.7	1.76	110/70		40.5	1575	78.4	3037	43.8	228	72	57	3.96	2.23	54	4	16
Hyperthyroid	9	53.2	1.51	130/73		58.0	2023	114.2	3981	44.5	292	106	47	6.27	3.93	58	6	12
Neurocirc. asthenia	6	64.9	1.69	115/75		41.8	1591	84.4	3192	45.3	224	78	57	3.90	2.32	49	4	15
Cardiac disease:																		
Plus form	7	58.9	1.58	171/105		51.8	1961	115.9	4479	50.0	*	*	*	*	*	*	19	21
Minus form	15	68.5	1.72	137/83		38.6	1509	71.4	2832	42.0	222	91	72	3.08	1.81	34	12	25
Combined	22	61.6	1.65	159/94		48.1	1782	95.9	3655	46.5	..	..	..	..	..	..	14	23
Hypertension compensated	5	61.0	1.60	190/103		44.0	1618	81.6	3020	42.4	258	84	58	4.46	2.62	53	8	13
Polycythemia vera	7	57.9	1.57	140/84		42.2	1571	167.7	6090	67.5	284	82	68	4.24	2.66	50	4	18
Anemia (varied)	6	63.1	1.60	124/74		49.8	1957	74.9	2938	30.0	249	77	54	4.63	2.76	60	8	13
Metabolic disorders	7	83.2	1.84	128/68		36.6	1589	69.3	2980	42.1	249	76	73	3.37	1.87	44	8	18
Avitaminosis	1	60.0	1.70	120/70		61.8	2180	95.3	3762	30.0	..	..	..	..	..	..	6	
Oblit. pul. arteritis	1	57.2	1.67	110/60		49.1	2813	91.4	5228	42.5	300	..	..	..	..	..	4	16

* Determinations not accurate because of orthopnea and marked dyspnea of patients.

If decompensation in the hypertensive progresses, both the right and left sides of the heart will show signs of failure. With beginning edema formation one notices a prolongation of both the arm-to-lung and arm-to-head circulation time. Most decompensated hypertensives show an increased circulating blood volume, an increased venous pressure and a normal or decreased cardiac output. They are of the dyspneic, orthopneic, cyanotic type with distended neck veins.

Infrequently one finds a hypertensive with a reduced blood volume. Such patients are not likely to be as dyspneic, orthopneic or cyanotic and present in many cases a different clinical aspect, especially from the therapeutic point of view. This has given the impetus for the classification of decompensated cardiacs into two general divisions, one with *increased blood volume*, such as decompensated hypertensives, called the *plus form* of decompensation; and the other with *decreased blood volume*, the *minus form*, of decompensation seen typically in recurrent endocarditis and recurrent rheumatic mitral conditions. In the minus form of decompensation the patient usually has a somewhat increased venous pressure, a normal circulation time and a low normal or decreased cardiac output. He does not require much propping up in bed.

The practical importance of the distinction between plus and minus forms of decompensation is in therapy. Certain drugs, such as morphine, are known to reduce blood volume and (other things being equal) they are therefore contraindicated in cases in which the blood volume is already reduced. Conversely, drugs like adrenalin, caffeine and pituitrin cause an increased blood volume, and are likewise contraindicated in the treatment of those heart failures connected with increased blood volume—the plus form of decompensation so common in hypertensives, and so on.

A further distinction that the classical studies of the cardiodynamic factors have helped clarify is that between central and peripheral failure. Peripheral failure is best exemplified by the condition of shock and collapse seen postoperatively, or in connection with injury or acute nervous disorders. The difficulty is essentially a failure of the return of venous blood from the periphery to the central pumping station, the heart. The peripheral constriction is accompanied by stagnation of blood in the dilated splanchnics. The circulating blood volume, the venous pressure and the cardiac output are all reduced. The heart must pump more frequently to receive the required amount of oxygen, a fact which explains the almost constant tachycardia. The state of shock or collapse is thus seen to be similar in many respects to the minus form of decompensation. The differentiation is very simple, however. In shock the splanchnic tone is not maintained, the venous pressure is zero, the blood pressure is low; while in the minus form

of decompensation the splanchnic tone is maintained without fall in blood pressure or venous pressure.

It is not suggested, of course, that if one has a clinical case of hypertension a complete cardiodynamic study should be made so as to better understand the patient's condition, or that a similar study should be made of a patient in shock. As mentioned above, the classic studies are of historic significance, and once established, they need no repetition. There are, however, certain clinical conditions where cardiodynamic studies are of present-day practical value.

For example, one of the most constant manifestations of beginning heart failure is increase in the venous pressure.[3] The method of visualization of the neck veins that Lewis[10] recommends may be sufficient to give one a rough estimate of the venous pressure, but where this would be most useful (*i. e.*, as the only definite sign in incipient cardiac failure), a more accurate method, such as the direct venipuncture detailed in the earlier section should be used. Figures above 8 cm. which are not due to extracardiac factors indicate circulatory embarrassment (Table 2, which shows an average venous pressure of 12 in the minus form of cardiac decompensation and of 19 in the plus form).

Although it is not often useful to differentiate decompensation into failure of the left or of the right heart because pure failure of either type is infrequently encountered clinically, there are occasions in which this differentiation is of importance. This is particularly true when we know the natural sequence of failure in certain clinical conditions—that left-sided failure in hypertension precedes and progresses to right-sided involvement also. It is then very much worth while to do the circulation time by two methods, one which will show the arm-to-lung time (the right heart), the other, the arm-to-head time representing the speed of circulation through right and left hearts. A subtraction of the first from the second time gives a fair idea of the relative speed of the two heart circuits. Although this subtraction does not yield figures that are absolutely diagnostic (since there is such variation in the normal limits of circulation time), an approximate idea of the speed through the heart and lungs can be obtained.

There is another condition in which we have found the cardiodynamic studies of definite clinical value and have recently reported upon this.[2b] Clinically cases are encountered which closely simulate hyperthyroidism but which are in truth neurocirculatory asthenia or incipient tuberculosis (especially in asthenic individuals with labile vasomotor systems). In many of these non-thyroid cases, as Lahey[9] has reported, the basal metabolic rate is raised to as high as 40 or 50, so that the B.M.R. cannot be relied upon in a diagnosis of borderline thyrotoxicosis. A more reliable indication of hyperthyroidism is the altered cardiodynamics. We have found in our

true hyperthyroid cases a markedly increased cardiac output, increased blood volume and increased speed of circulation (Figs. 3, 4 and Table 2). In the metabolism of the hyperthyroid individual, in spite of increased oxygen consumption, there is a diminished utilization of oxygen by the tissues, expressed by a diminished arteriovenous oxygen difference. From the formula cardiac output $= \frac{\text{oxygen consumption}}{\text{a-v oxygen difference}}$ we see we must have an increased cardiac output. In fact, the cardiac output in hyperthyroidism averages about 6.27 liters, as compared to the normal of 3.96 liters. The blood volume too is raised to an average of 114 cc. per kg., where the normal is 78.4 cc. per kg. The circulation time is usually reduced from the 16 seconds normal to about 10 seconds, because of the need for active, rapid circulation. This helps compensate for the reduced power of the tissues to utilize the oxygen brought to them, reflected by the diminished arteriovenous oxygen difference (av., 47 cc.). In contrast to the above, we note that in cases of neurocirculatory asthenia or incipient tuberculosis, the diseases not being metabolic, the cardiodynamic factors remain normal. Although they may have an increased oxygen consumption there is no change in the other factors. We feel then that cardiodynamic studies are of definite aid in the clinical differentiation of borderline hyperthyroid cases, and that if the facilities for doing the cardiac output are not present, at least circulation time and blood volume determinations should be made.

We have further had the occasion to utilize the cardiodynamic studies in an unusual case of obliterating pulmonary arteritis which closely resembled thyrotoxicosis clinically (*i. e.*, B.M.R. was +37).[14] The perfectly normal blood volume and circulation time helped rule out the possibility of hyperthyroidism (Table 2).

As reference to Table 2 would show, perhaps the most important clinical use of blood volume studies is in the diagnosis of polycythemia. Even clinically it is difficult at times to differentiate the polycythemia vera from the symptomatic. Their natures, of course, are entirely different; the true polycythemia being a hyperplastic blood disease, and the symptomatic a manifestation of difficulty of aëration, stagnation and hypertension in the pulmonary circuit. In true polycythemia we get the very highest blood volume and hematocrit readings. *The hematocrit is at least as important as the increase in blood volume.* We must demonstrate that the increased blood volume is not due to any appreciable increase in plasma, but to increase in the cellular content of the blood before we can call it a true polycythemia. Thus with blood volume above 7000 total (4300 cc. per sq. m. of body surface), and hematocrit readings above 55%, we know we are dealing with a polycythemia vera. The symptomatic polycythemias fall below these figures (Table 2).

It is interesting to note that in spite of the increased blood volume

in polycythemia there are no other disturbances in the cardiodynamic factors except for a slightly prolonged circulation time.* The increased viscosity of the blood evidently produces a slower blood flow. The cardiac output remains normal, but it takes the blood longer to make one complete revolution, *i. e.*, there is prolongation of the "*revolution time.*"[2a]

It is of great importance to do a total blood volume and hematocrit reading in cases of polycythemia vera. For clinical purposes, if the facilities for the former are not present, at least the hematocrit reading should be obtained.

Summary. The factors maintaining circulatory equilibrium, cardiac output, blood volume, venous pressure, blood pressure and circulation time) are defined and discussed.

Historically the importance of cardiodynamic studies in explaining the nature of, and circulatory mechanisms involved in certain clinical conditions such as hypertension, central *vs.* peripheral failure, right *vs.* left heart failure, hyperthyroidism and polycythemia are stressed.

It has been found useful from the diagnostic and therapeutic points of view to group decompensated cardiacs into plus and minus forms of failure, based on blood volume readings.

From the practical viewpoint, the greatest uses made of cardiodynamic studies are in the following:

1. Borderline cases of hyperthyroidism, where an increased cardiac output, increased blood volume and rapid circulation time distinguish this condition from neurocirculatory asthenia or incipient tuberculosis (in which the above values are normal).

2. In polycythemia vera, the very high blood volume and hematocrit reading is usually sufficient to distinguish it from the symptomatic polycythemias, which do not yield such high figures.

3. In the differentiation between right and left heart failure, aside from clinical differences, the lengthened arm-to-lung circulation time in right-sided failure is of distinct value. By subtracting the arm-to-lung circulation time from the total pulmonary circulation time (arm-to-head) one can estimate the speed through the left heart circuit.

4. In decompensation, often the very first sign of right heart failure is an increase in the venous pressure.

REFERENCES.

(1.) **Barcroft, J.**: J. Physiol., **73**, 344, 1931. (2.) **Goldbloom, A. A.**: (*a*) Determination of Basal Cardiac Output From Blood Volume Studies (unpublished data); (*b*) Med. Clin. North America, **17**, 279, 1933; (*c*) Internat. Clin., **3** (Ser. 46), 205, 1936. (3.) **Goldbloom, A. A.**, and **Bauer, H. E.**: Coll. Papers New York Homeopathic Med. Coll. and Flower Hosp., **1**, 45, 1934–35. (4.) **Goldbloom, A. A.**, and **Libin, I.**: Arch. Int. Med., **55**, 484, 1935. (5.) **Grollman, A.**: The Cardiac Output of Man in Health

* Our results are in disagreement with Tarr, Oppenheimer and Sager,[15] who found a moderate to marked prolongation of circulation time in polycythemia.

and Disease, Springfield, Ill., Charles C Thomas, 1932. (6.) **Hitzig, W. H.**: Am. Heart J., **10**, 1080, 1935. (7.) **Hochrein, M.**, and **Keller, J.**: Arch. f. exper. Path. u. Pharmakol., **164**, 529, 1932; **166**, 229, 1932. (8.) **Keith, N. M., Rowntree, L. G.**, and **Geraghty, J. T.**: Arch. Int. Med., **16**, 547, 1915. (9.) **Lahey, F. H.**: New York State J. Med., **32**, 1341, 1932. (10.) **Lewis, T.**: Diseases of the Heart, New York, The Macmillan Company, p. 9, 1933. (11.) **Mautner, H.**, and **Pick, E. P.**: Arch. f. exper. Path. u. Pharmakol., **97**, 350, 1923. (12.) **Rein, H.**: Klin. Wchnschr., **12**, 1, 1933. (13.) **Robb, S. P.**, and **Weiss, S.**: Am. Heart J., **8**, 650, 1933. (14.) **Rothschild, M. A.**, and **Goldbloom, A. A.**: Arch. Int. Med., **61**, 600, 1938. (15.) **Tarr, L., Oppenheimer, B. S.**, and **Sager, R. V.**: Am. Heart J., **8**, 766, 1933. (16.) **Taylor, A. A., Thomas, A. B.**, and **Schleiter, H. G.**: Proc. Soc. Exp. Biol. and Med., **27**, 867, 1930. (17.) **Wollheim, E.**: Ztschr. f. klin. Med., **116**, 269, 1931.

MOVEMENTS OF ROENTGEN-OPAQUE DEPOSITS IN HEART VALVE AREAS.

II. The Excursion of the Apex and Base of the Left Ventricle Compared With that of the Left Border.

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In 1937 we published a study based upon roentgenkymograms of Roentgen-opaque deposits in heart valve areas.[35] At that time our material consisted of 3 cases, in 1 of which there was calcification of the mitral valve (proved by necropsy) and in the other 2, involvement of the aortic valve area. The technique used and the important limitations of the method were described. In all 3 cases there was an extensive movement of the Roentgen-opaque masses toward the apex during systole. It had been pointed out by Dietlen[1] as long ago as 1910 that during systole the cardiac apex moves upward and inward toward the base. We had frequently observed this phenomenon in patients in whom the apex was visible above the diaphragm and had made several roentgenkymograms of the apical movement. Unfortunately, however, none of the 3 patients with calcified valves could be placed in positions in which the apex was visible above the diaphragm (probably because of the fact that all had cardiac enlargement). We were unable therefore to make roentgenkymograms of the apex for comparison with the movement of the calcified areas. Nevertheless, we regarded the evidence at hand as adequate to support the conclusion that the important feature of left ventricular contraction is shortening of the long axis and that furthermore, not only does the apex move toward the base, but the base moves toward the apex. Compared with the

movement of Roentgen-opaque masses in the 2 cases in which kymograms of the left border were also made, it appeared that the movement of the left border was of much less extent than that of the apex and base. The effect on auricular filling of this unexpectedly great movement of the base during ventricular systole was also discussed.

In the last 18 months we have studied 2 more cases with Roentgen-opaque masses in the region of the aortic valve, dense enough to show satisfactorily in roentgenkymograms. In 1 of these the findings were practically identical with those of Cases 2 and 3 of our former paper and therefore need not be presented. The other case was unusual in that, despite the presence of a fairly dense calcium deposit in the region of the aortic valve (Fig. 1), the heart was not enlarged, and there were no clinical signs of aortic valve disease. This suggested that the calcium did not involve the leaflets to any great extent and was probably in the neighborhood of their attachments. The cardiac apex could be separated from the diaphragm by having the patient take a deep breath.

A roentgenkymogram was made with the patient placed in such a position of recumbency that movement of the apex and the calcium deposit toward and away from each other could be seen through the horizontal slit of the roentgenkymograph with the Roentgen ray beam centered halfway between the calcium mass and the apex. It was possible in this manner to include movement of both the calcium deposit and the apex in one exposure. The kymogram was made according to the technique we have described previously,[3a] and was timed by a simultaneously recorded electrocardiogram. A roentgenkymogram timed by an electrocardiogram was also made of the left ventricular border.

The results of the studies are shown in Figures 2 and 3. It may be seen that very early in systole, the calcium deposit begins to move abruptly toward the apex as it did in the other 4 cases. At almost the same instant, movement of the apex toward the base begins. Both of these movements continue during systole; the excursions are comparatively wide. In Figure 3, the much smaller excursion of the left ventricular border is seen. In early ventricular systole when the apex and base are moving rapidly toward each other, the left ventricular border is actually moving outward instead of inward.* It does not recover the ground lost until nearly the middle of systole, but the slow inward movement begins after the initial outward movement and continues during the remainder of systole.

* Outward movement of the left border is the rule during the early part of ventricular systole. This movement, although due to ventricular contraction, is a resultant of changes in shape and size of the ventricles and movements of the heart as a whole, such as rotation. The complexity of the movements makes attempts to evaluate the importance of each factor uncertain in result. At any instant, they may tend to move the border in the same direction or in opposite directions.

FIG. 1.—Roentgenogram of the patient in the left oblique position. This view was selected because it best demonstrates the extent of the calcium deposit (indicated by arrows). The separation of the heart from the diaphragm is not seen with the patient in this position. During exposure the print was subjected to "dodging" to improve contrast in the region of the valves.

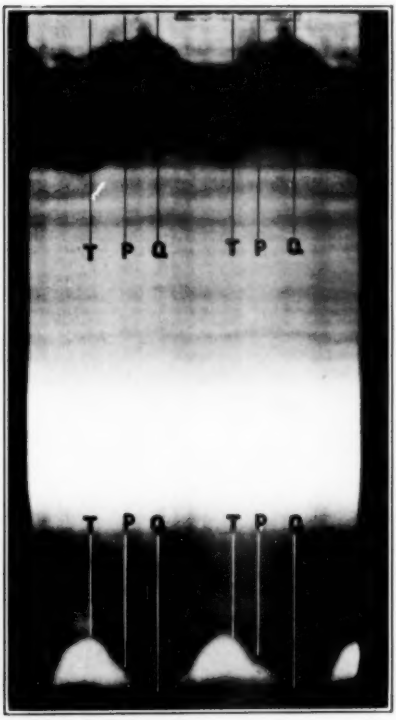

FIG. 2.—Roentgenkymogram with the patient in the dorsal recumbent position with right side facing the horizontal slit. Movements of the calcium deposit in the aortic area and of the apex toward each other during systole and away from each other during diastole. The calcium deposit is shown at the top of the print and the apex at the bottom (impinging slightly on the diaphragm at the end of diastole). The sequence is from left to right. *T* corresponds to the end of the *T* wave of the electrocardiogram and *P* and *Q* to the beginning of the *P* and *T* waves respectively. During exposure, the print was subjected to "dodging" to improve contrast. The size of the print has been reduced 33% in reproduction.

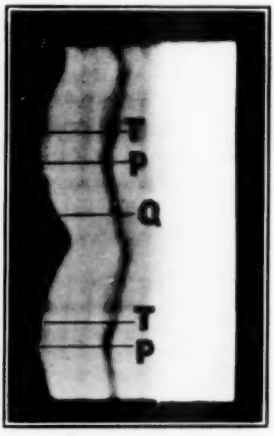

FIG. 3.—Roentgenkymogram of the left ventricular border made with the patient in the antero-posterior position in order to record lateral movement. The level was nearer the apex than the base, approximately 2 cm. above the diaphragm. *T*, *P* and *Q* refer to the same electrocardiographic events as in Figure 2. The sequence is from top to bottom. The size of the print has not been altered in reproduction.

Recently we have made fluoroscopic studies of a patient in whom the part of the right coronary artery lying in the auriculo-ventricular groove was seen to be calcified. During ventricular contraction this part of the artery and the apex moved toward each other. We regarded this as evidence that the auriculo-ventricular groove was being pulled toward the apex.

Discussion. In addition to the limitations of the method and the precautions that must be observed in the interpretation of results which were discussed in our former paper, there are still other factors to be considered in studies such as that shown in Figure 2. The centering of the Roentgen ray beam halfway between the calcium deposit and the apex, and the spatial relations of these areas to the position of the target and film, influence, to at least a slight extent, the magnitude of the recorded movements. The two chief factors, however (divergence of rays and lack of parallelism between the slit and the long axis of the heart), tend to counterbalance each other. A calculation of the maximum possible error which could occur from these sources indicates that it is small, and can be disregarded in the present discussion.

The conclusion reached in our former paper that the important movement of the left ventricle during contraction is shortening of the long axis with extensive movement of the base and apex toward each other is confirmed by the findings in this case. Likewise, it is shown that the movement of the left border is a relatively small part of the cardiac movement and that, as a matter of fact, this part of the heart border may be moving outward during at least part of the period of contraction. It would therefore seem justifiable to conclude that roentgenkymography of the left ventricular border may fail to reflect the most important part of movement during contraction.

The fact that in each of the 5 cases we have studied there has been an extensive movement of the calcified tissues toward the apex (the present case showing less than any of the others) tends to confirm the view previously expressed regarding auricular filling. The floor of the auricles must be pulled downward during ventricular contraction, along with the calcium-bearing tissues at the base of the ventricles. This movement would tend to fill the auricles by forcible suction. We have no means of estimating with any accuracy the part this process plays in auricular filling but it seems to be an important factor. The marked emptying of the cervical veins which occurs during ventricular systole (easily demonstrated by optically recorded phlebograms timed by some cardiac activity such as is represented by the electrocardiogram) suggests that the floor of the right auricle is also pulled downward during ventricular systole.*

In addition to the forcible filling of the auricles that must occur

* This explanation for the sharply descending wave in the jugular phlebogram during ventricular systole is not new. It has been discussed by Wiggers.[3]

during ventricular systole, the relaxation of the ventricles during diastole and the upward movement demonstrated in the calcium-bearing tissues, suggests that this process under certain circumstances may also aid in ventricular filling.*

One effect of forcible systolic pull of the root of the aorta toward the apex is that the blood does not have to be propelled quite so far during systole to enter the aorta as it would if the aortic valve were fixed in position. Roentgenkymograms of the ascending aorta occasionally show an inward movement of the aortic wall just before the outward thrust of the pulse. A similar phenomenon is occasionally observed in carotid pulse tracings. It now seems probable that this preliminary wave is due to downward pull on the root of the aorta beginning during the isometric contraction phase. The major part of the downward pull, however, occurs during ejection. To what extent it may alter the contour of the pulse wave is not certain. It is probable nevertheless, that one of its effects is to lessen the impact of the blood on the aortic wall.

Summary. A cardiac roentgenkymogram timed by an electrocardiogram was made in such a way as to demonstrate the movements, toward and away from each other, of the apex and of a calcium deposit in the region of the aortic valve. From the data obtained in this case and 4 others (3 previously published) in which roentgenkymograms were made of calcium deposits in either the mitral valve or aortic valve area, the following points are emphasized.

1. The change in size and shape of the left ventricle during contraction is probably due more to shortening of the long axis than to movement of the lateral wall.

2. The floor of the auricle (roof of the ventricle) does not remain in a relatively fixed position as is usually assumed, but is pulled vigorously toward the apex during ventricular systole, while the apex is moving toward the base. The directions of movement are reversed in diastole.

3. The movements of the left ventricular border are much smaller than the movements of base and apex. The shortening of the long axis may be so great that the left border actually moves outward during the early part of systole. The foregoing facts should be taken into consideration in any attempt to study ventricular contraction by means of recording the movements of the left ventricular wall. These movements may fail to reflect the vigor or extent of the left ventricular contraction.

* It would be difficult to understand how hearts almost completely encased in calcium and therefore capable of little or no external movement could continue to function otherwise. The vigorous downward pulling of the tissues between the auricles and ventricles during systole (helping to fill the auricles and empty the ventricles) and upward movement during diastole (helping to empty the auricles and fill the ventricles) is probably an essential part of the mechanism which permits the patient to survive until the external walls of the heart are relieved of some of their restriction by operation.

4. The marked movement of the auricular floor, as a result of ventricular contraction, must create a powerful suction which is an important factor in bringing about auricular filling.

5. It is probable that when movements of the external walls of the heart are restricted, the filling and emptying of its chambers are made possible by the effects of ventricular contraction and relaxation on movement of the tissues separating auricles and ventricles.

REFERENCES.

(1.) **Dietlen, H.**: Ergebn. d. Physiol., **10**, 598, 1910. (2.) **Wiggers, C. J.**: The Circulation in Health and Disease, Philadelphia, Lea & Febiger, p. 231, 1923. (3.) **Wolferth, C. C.**, and **Margolies, A.**: (*a*) Am. Heart J., **10**, 425, 1935; (*b*) Trans. Assn. Am. Phys., **53**, 346, 1937.

HISTOLOGIC INVESTIGATION INTO THE PYLORIC GLAND ORGAN IN PERNICIOUS ANEMIA.*

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The present histologic investigations into the pyloric gland organ in pernicious anemia in man form a continuation of earlier work by Meulengracht *et al.*[16a–f,17,18] carried out in this Clinic on the localization of the anti-anemic factor ("intrinsic factor") demonstrated by Castle in the stomach.

We learn from this earlier work that the pig's stomach, both histologically and functionally, is divided into two distinct parts: a fundus portion, containing fundus glands with parietal and chief cells secreting hydrochloric acid and pepsin (rennin), and a pyloric portion, containing pyloric glands with the large clear pyloric gland cells secreting the anti-anemic factor. We further learn that an anti-anemic activity, demonstrated in the duodenum, must be attributed to Brunner's glands, which, histologically, are identical with the pyloric glands, so that both sets of glands must—at least in this respect—be regarded as constituting a functional entity, and it was suggested to give them the common name, *pyloric gland organ*.

As the investigations showed that it is the pyloric gland organ which produces the anti-anemic factor of the stomach, one might reasonably assume that this organ becomes atrophic or for some other reason does not function in pernicious anemia; it was therefore decided to undertake a histologic examination of the pyloric gland organ in patients with pernicious anemia.

Earlier Investigations. There exist numerous investigations into the histology of the stomach and, to some extent, of the intestine,

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in pernicious anemia. They were started as far back as 1870 by Fenwick,[7] who demonstrated atrophy of the gastric mucous membrane. Since then, as mentioned, numerous investigations have been undertaken. Those of Faber and Bloch,[6a,b] Lange,[14] and Wallgren[24] may be regarded as the most important, because the material used was fixed according to Faber and Bloch's method[6a,b] by means of intraäbdominal formaldehyde injections immediately after death. The material is thus protected against postmortem changes which damage the histologic picture. The numerous histologic investigations show that the stomach itself is always the seat of a severe gastritis with interstitial changes in pernicious anemia, most pronounced in the fundus portion where there is atrophy of the glands and destruction of the specific glandular elements, namely, the parietal and chief cells. The changes seem to be less striking in the pyloric portion, but more detailed information of this region is not available. Our knowledge of the condition of Brunner's glands is extremely scanty. In the histologic descriptions of the individual cases in the works of Faber and Bloch,[6a,b] as well as those of Lange,[14] remarks may be found, such as: that the interstitial changes in Brunner's glands are small, or that Brunner's glands seem relatively well preserved, or that Brunner's glands appear normal, and so on, but more detailed information is not given. One gets the impression that attention has not been especially directed to this point.

At the International Hæmatological Congress in Münster, held in 1937, I[16f] communicated the first results of my histologic investigations into the pyloric organ in patients with pernicious anemia, from which it appeared that the pyloric and Brunner's glands seemed surprisingly well preserved, an observation which was confirmed in 1938 by Magnus and Ungley.[15]

Author's Investigations. *Material.* During the last few years I have collected 9 stomachs with the corresponding duodenums from patients diagnosed as cases of pernicious anemia. These patients had died either from pernicious anemia, having been admitted to hospital *in extremis*, or from intercurrent diseases, their anemia being more or less compensated.

In 8 of the cases, the diagnosis was confirmed by the characteristic course of the disease, with a typical blood picture, gastric achylia and by subsequent response to specific therapy. The clinical diagnosis was very doubtful in 1 case, and the postmortem findings made the diagnosis still more doubtful; in fact, the subsequent histologic investigation of the stomach places this case in a class by itself.

Technique. The organs of all the 9 cases examined were fixed immediately after death by the method of intraäbdominal injection of formaldehyde, devised by Faber and Bloch.[6a, b] Different concentrations and amounts can be used, but my impression is that the best material is obtained by using a greater amount of a little weaker solution. The following scheme

was adopted: 600 cc. of 5% formaldehyde solution were injected in 5 different situations, where the stomach and duodenum were thought to be. The aim was to inject some of the fluid into the stomach, and in some cases excellent fixation was obtained, to the exclusion of postmortem changes of a digestive or other nature, but in other cases the result was not very good, probably largely because the fluid did not enter the stomach. Still larger amounts of fluid ought perhaps to be used. The organs were removed after death and kept in the fixing fluid.

For the histologic investigations the stomach and duodenum were opened along the greater curvature and a series of sections were cut along the greater curvature and duodenum as far as the jejunum.

The material was prepared in the manner of "collared beef," that is to say, strips were cut out, longer or shorter according to their thickness, which were then rolled up like collared beef, tied together with thread, embedded, and when cut in this form each section contained a long piece of the stomach wall. In successful cases, one section will include 10 to 20 cm. or more of stomach wall.

Hematoxylin-eosin, hematoxylin-Congo red and Unna's polychrome methylene blue were used for staining.

The preparations were subjected to a qualitative investigation, but so far it has not been possible to examine them quantitatively.

The Normal Stomach. I feel justified in placing the Danish investigations, especially those of Bloch,[2] Lange,[14] and Vimtrup[23] before other studies, because they were done on well-fixed material and because they made use of the stomachs of children and adults, where as far as possible it was ascertained beforehand that the subjects had normal stomachs. The best and most extensive investigations are attributable to Lange,[14] in whose monograph the normal structure and amount of the various glands and interstitial tissue were investigated and described. They have to some extent been made accessible to a wider public by Faber.[5]

From these investigations, especially those of Lange,[14] we have an accurate knowledge of the histology of the normal stomach. The descriptions agree with what I have been able to observe in my own normal material. Some of the chief points may be mentioned.

In the fundus of the normal stomach, the glands are closely packed together in palisade fashion. Above are found the gastric crypts covered with the surface epithelium; they occupy about one-fifth of the thickness of the mucous membrane. The fundus glands constitute the lower two-thirds, in the upper part of which the parietal cells with their eosinophil cytoplasm are especially prominent, while the chief cells with their basophil granular cytoplasm mainly occupy the basal part. The glands are placed so closely together in palisade fashion, as has been mentioned, that there is practically no interstitial tissue; only a very few connective tissue cells belonging to the tunica propria, and a very few round cells, chiefly lymphocytes, are found. In the pyloric portion the crypts are longer, the glands are of a slightly different structure, they are not quite so closely packed, and they tend to branch into

alveoli down toward the muscularis mucosæ. The type of cell here is the large clear pyloric cell, which lines the branching lumina of the gland down to the muscularis mucosæ. The interstitial tissue is still scanty, but more abundant than in the fundus. The cells are connective tissue cells belonging to the tunica propria, and a few round cells, mainly lymphocytes. A solitary flat lymphoid follicle is very rarely found just above the muscularis mucosæ in the fundus and in the pyloric portion.

The picture changes on the other side of the pylorus: the mucous membrane is now typical intestinal mucous membrane, with cuticular cells and goblet cells; and at the bottom of the Lieberkühn crypts, Paneth cells are seen. There is abundant interstitial tissue, with numerous round cells in the intestinal mucous membrane. Under the muscularis mucosæ, Brunner's glands are seen spreading out in the submucosa. They occur as closely packed gland lumina, lined with large clear cells of the same shape and appearance as the pyloric gland cells; the lumina lie so tightly packed together that there is practically no interstitial tissue. The cells seen are only an occasional tunica propria connective tissue cell and a very few round cells.

The various types of glands are distributed in the human stomach in the following manner: around the esophageal opening there is a narrow band, a few millimeters broad, of so-called "cardiac glands," which mostly resemble dislodged pyloric glands (compare the arrangement in the pig); next comes the large fundus portion, which only contains fundus glands. Then near the pylorus there is a smaller region which only contains pyloric glands. According to Buechner[3] and Paschkis and Orator,[19] they extend for about 6 cm. into the stomach from the pyloric ring along the lesser curvature. At the pylorus the pyloric glands commence to dip down under the muscularis mucosæ, and are then continued as Brunner's glands in the submucosa; they are largest and most compact just past the pyloric ring, but gradually diminish in size and numbers and disappear at about 10 to 20 cm. from the pylorus. They extend therefore a good distance beyond the ampulla of Vater.

The Stomach in Pernicious Anemia. On examination, the 8 stomachs from cases of pernicious anemia in which the diagnosis had been made absolutely certain by clinical investigation and autopsy findings, all showed, on the whole, similar changes.

The Fundus Region. *The Surface Epithelium and the Crypts.* In places where fixation was imperfect, it was often difficult to form a definite opinion of the condition of the surface epithelium; but where the fixation was successful it appeared to be well preserved, though frequently the cells were shorter, more cubical, than normal. Round cell infiltration was a little more marked than normal, but was not very pronounced.

The crypts were often considerably shorter than normal, and

they were more widely separated from one another by more abundant interstitial tissue. This was especially the case when there was atrophy of the mucous membrane; and if the atrophy was pronounced the crypts largely disappeared, in fact they might be entirely deleted, so that the mucous membrane presented a smooth, even surface, covered by somewhat flattened surface epithelial cells.

In some situations the surface and crypt epithelium was replaced by typical intestinal epithelium, with cuticular and goblet cells, and at these points ducts of glands penetrated the mucosa down to the muscularis mucosæ, of the same form and appearance as the Lieberkühn crypts, with Paneth cells at the bottom. The portions covered by the intestinal type of epithelium took the form of islands, "intestinal islands." Metaplasia of the gastric mucosa into intestinal mucosa had occurred here. Intestinal islands, which are a well-known phenomenon in all forms of chronic gastritis, were found in 7 of the 8 stomachs.

The Fundus Glands. While, as mentioned above, the fundus glands are placed regularly close together in palisade fashion in the normal stomach, in the 8 stomachs examined they were separated from each other by a considerable amount of interstitial tissue, and their structure was entirely different so that they could no longer be recognized as fundus glands. They were, as a rule, irregularly tortuous and branching. Clusters of very small atypical gland lumina were often seen lying together. In other situations also or in other stomachs lumina could be seen which were more or less dilated into cysts. A cystic dilatation of the gland lumina was a very characteristic phenomenon in some of the stomachs ("cystic gastritis"). The glandular epithelium was entirely altered in character. The parietal cells had quite disappeared, nor could the chief cells with the basophil properties be recognized, at least not with any certainty. In place of these two specific types of epithelial cells, the gland lumina were lined with an undifferentiated epithelium, the cells of which varied greatly in shape and height, in the small lumina being a little higher and in the cystic dilated lumina often quite flat; the nuclei and cytoplasm presented no special characteristics.

The Interstitial Tissue. The interstitial tissue was, as stated, greatly increased in amount, because of the accumulation of closely packed cells. In comparison with the normal stomach, where the palisades of closely packed fundus glands barely leave room for a single cell in the interstitial tissue, this was strikingly the most obvious change. The increase only to a very small extent involved connective tissue. The characteristic feature was the broad compact belts of round cells, which insinuated themselves between the irregular, deformed gland lumina and up between the crypts. The main types of cells were lymphocytes and plasma cells. The lymphocytes were only sparsely distributed in the interstitial tissue.

the greater part of them being aggregated in lymphoid follicles. In some cases these were exceedingly numerous ("follicular gastritis"), while in other cases they were less abundant; but they were always a striking feature when compared with the histologic appearance of the normal stomach, where they are, as mentioned, scarce. They were always situated low down near the muscularis mucosæ, but from here they might extend up through practically the whole thickness of the mucosa. The interstitial tissue in their neighborhood contained a more liberal supply of lymphocytes. Otherwise, plasma cells were the predominant type in the interstitial tissue. They had the characteristic nuclei and the abundant strongly basophil cytoplasm, and lay in dense masses everywhere in the mucosa between the gland lumina. Neutrophils were very rare. Very frequently large cells were seen with small dense nuclei and abundant eosinophil and somewhat granular cytoplasm (Russell bodies). This type of cell is nearly always found in chronic gastritis, and is regarded as a phagocytic cell.

As a result of the aforesaid changes there was a definite atrophy of the whole mucous membrane in most of the cases. It was sometimes quite thin, with a smooth surface and scanty glandular elements. It must be recognized, however, that this appearance may have been partly an artefact. Thus parts of the stomach were observed which had been fixed in a greatly dilated condition, so that the whole wall was quite thin, and other parts which had been fixed while greatly contracted, the whole of the wall being quite thick. In the former situations a thin and smooth mucous membrane, apparently completely atrophied, was seen microscopically, while in the contracted portions the mucous membrane seemed to be heaped up, appeared thicker and did not give the same immediate impression of atrophy. An estimate of the thickness and atrophy of the mucous membrane must therefore be made with reserve, and with reference to the state of contraction; the best guide is the thickness and structure of the muscularis mucosæ in the particular preparation. On taking these points into consideration, I believe that in all the cases I have been able to ascertain that there was some degree of atrophy of the mucous membrane in the fundus.

The Pyloric Region. On passing from the fundus to the pylorus the gastritic changes in the 8 stomachs gradually diminished; they were still present, but less pronounced. This was the chief impression conveyed.

The Surface Epithelium and the Crypts. The surface epithelium appeared to be well preserved. It did not seem to be at all flattened. There was little or no change in the cells. Metaplasia to the intestinal type of epithelium was not observed. Here also the *crypts* were a little more separated from one another than in the normal stomach, because of the somewhat greater amount of interstitial

tissue, but this was not very marked. The length and appearance of the crypts seemed normal.

The Pyloric Glands. On account of the slight increase in interstitial tissue, the glands here also were more widely separated than normal, but otherwise their normal form and appearance was preserved. There was no distortion or process of repair, and no cystic enlargement; in the vicinity of the muscularis mucosæ where the glands form crypts, the apparently uniform gland lumina were found in the usual small groups of small lobuli. It is possible that in some of the cases they showed a slight reduction in number and extent, but I have not been able to demonstrate any great diminution. The different gland lumina were normal in appearance, and the cells exhibited the same abundant clear cytoplasm as normal ones, with the same finely reticular structure, and a round or oval nucleus usually situated toward the base. As in the normal stomach, the pyloric glands were most numerous in the vicinity of the pyloric ring.

The Interstitial Tissue. To ascertain whether or not this was pathologically increased was a little more difficult here than in the fundus, because there is normally more interstitial tissue with more cells in the pyloric portion than in the fundus, where, as mentioned, there is hardly any to be found. There is nevertheless no doubt that the interstitial gastritic changes in all the cases extended into the pyloric region; there was perhaps a small increase in the connective tissue, but here also it was especially the cells which were increased. Again the cells were mainly lymphocytes and plasma cells; the lymphocytes had the same tendency as in the fundus to collect in lymphoid follicles, which were abundant, or in dense belts which resembled follicles. The plasma cells were more scattered among the crypts and glands. In most of the cases there were occasional Russell bodies.

The Duodenum. When we come to the intestinal mucous membrane of the duodenum just past the pylorus, it is very difficult to be certain whether the inflammatory changes reached this point. The interstitial tissue of the intestinal mucosa is normally so rich in cells that it is difficult to recognize a small increase in the number or a slight alteration in the type of cell. A very thorough preliminary study of the normal mucous membrane of the duodenum is essential.

Mucosa. On examining the mucosa of the duodenum in the 8 cases of pernicious anemia nevertheless, one quickly realized, in spite of the above reservation, that no great change could have occurred. The coarser structure, with valvulæ Kerkringii and intestinal villi, was not markedly altered; the thickness of the mucous membrane appeared normal; the crypts of Lieberkühn seemed to be of normal structure and length, and were lined by cuticular cells and goblet cells and with Paneth cells at the base.

A superficial examination of the amount of interstitial tissue and type of cell did not show any demonstrable deviation from the normal.

Brunner's Glands. Interest is centered primarily on Brunner's glands, and the findings in the main were similar in all the 8 cases of pernicious anemia. Here also Brunner's glands made their appearance just beyond the pylorus, as in normal cases, and it was clear that it was the pyloric glands, which now began to dip down under the muscularis mucosæ, and spread out in the submucosa. In all the 8 affected stomachs they were found in the greatest numbers and the largest lobuli just below the pyloric ring, and for a distance of a few centimeters. In the present investigation, no attempt has been made to decide whether there has been any alteration in number and size, that is to say, any quantitative deviation, and all that can be said here perhaps is that at any rate the change was not striking. But this question will be taken up later in this discussion. With regard to the restricted qualitative investigation, the results in all the 8 stomachs were the same; histologically, no definite pathologic changes could be demonstrated.

The structure of the glands, with their closely packed uniform lumina forming lobuli of varying size in the submucosa, was normal. Each lumen was normal in appearance, small, and surrounded by a few tightly packed cells. With the staining method used, no histologic changes were seen in the actual cells; they were characterized by the usual abundant clear cytoplasm with the typical fine reticulate structure, and by the round or oval basal nuclei. Only in 1 case was I struck by the fact that the cells were flatter than normal, and the lumen thus a little larger. The cells were here less clear, the nuclei were found and were situated at the base, though more in the center of the cells. I do not know whether this is an altered functional condition or phase. Interstitially, there were only a few tunica propria cells between the closely packed gland lumina, and here and there an occasional plasma cell in the angles between the contiguous lumina, but this seems to be what is normally observed.

This was the picture seen in the 8 stomachs, but in the case of the ninth stomach (Case 9) there was some divergence from these findings.

This stomach also showed evidence of gastritis in the fundus, with considerable interstitial changes. The fundus glands were somewhat atypical and atrophied, but the atrophy was very much less pronounced, and there were a good number of apparently well-preserved parietal cells, which reached as a belt in the mucous membrane from the base of the crypts to a little distance above the muscularis mucosæ, where they were replaced by cells which resembled typical chief cells. In the pyloric portion there was slight gastritis, but an

apparently well-preserved gland system. Brunner's glands seemed quite normal.

The presence of fairly well-preserved parietal and chief cells was thus quite unusual.

A review of the clinical case sheet and the postmortem report, however, strongly suggested that it was not a case of true pernicious anemia (see case report).

If therefore we confine ourselves to a consideration of the findings in the 8 stomachs, where the diagnosis of pernicious anemia can be regarded as being definitely established both clinically and pathologically, we can summarize the results as follows:

All the cases exhibited severe gastritic changes in the fundus, with atrophy of the fundus glands, and disappearance of the specific glandular elements, that is, the parietal and chief cells. The gastritic changes continued down into the pyloric portion, but they were obviously less pronounced there, and the pyloric glands seemed relatively well preserved, as also did the gland cells both in number and appearance. Finally, it may be said of Brunner's glands that they appeared absolutely normal, at any rate qualitatively.

The histologic changes were thus most marked in the region of the hydrochloric acid-producing and pepsin-producing fundus glands, but less marked in the pyloric gland region, and entirely absent in the vicinity of Brunner's glands.

Discussion. The result of the investigations was thus rather surprising and different from what I had expected, because it seemed probable that the chronic gastritis with atrophy of the glands would extend down to the pyloric gland organ and compromise its action. But we must acknowledge that the changes are mainly connected with the hydrochloric acid and pepsin-producing portion of the stomach, while the pyloric gland organ was moderately intact.

The question is now whether this affects the earlier investigations, the result of which was that the anti-anemic factor is produced by the pyloric gland organ.

I do not think that this is the case. The therapeutic experiments with different fractions of pig's stomach, on which this result was based, undoubtedly carry great weight. They have, moreover, been confirmed in Holland (Groen[10]), in Denmark (Gram[9]), in England (Ungley[22]) and in the U. S. A. (Thompson[21]). They are also supported by the broad experiment represented by the routine treatment of patients suffering from pernicious anemia with pylorus powder (pylorin), as it is carried out in Denmark. From material at this hospital, Alsted[1] has already shown that when using pylorus powder one-half the dose suffices, compared with the amount required when a powder of the whole stomach is employed. This has later been confirmed by very extensive daily experience.

One must therefore undoubtedly seek another explanation which

will bring the two series of investigation into harmony with one another.

It is thus possible, although my present impression is that it is *improbable*, that a *quantitative* examination of the pyloric gland organ in patients with pernicious anemia may disclose changes in the number and amount of the specific glandular elements.

It is expected that Danish histologic investigations will be available shortly which will establish a normal basis for comparison of the glandular elements in this region.

The possibility of a *functional insufficiency* should also be kept in mind in future investigations. The functional capacity of an organ cannot be determined from its anatomic condition alone. There is really nothing to prevent a pyloric gland organ, anatomically intact or only slightly affected, from having its function impaired for some other reason. In this connection it is worth while to bear in mind the conditions in diabetes. It has been established beyond doubt that the pancreas islands produce insulin and that its production is reduced in diabetes, and yet search as to whether or not there is atrophy of the pancreas islands in diabetes yielded conflicting results. It is also expedient to draw attention to Goldhamer's[8] experiments which indicated that it was the *volume* of the gastric fluid which was reduced in pernicious anemia, while the anti-anemic activity per unit volume was the same as under normal conditions. The gastric fluid was obtained by continuous suction, and it was found that, while the amount of secretion in normal persons averaged 150 cc. per hour, the mean volume was 20 cc. per hour in patients suffering from pernicious anemia. It was found that there was a relation between the amount of gastric juice and the number of red blood corpuscles, and when the gastric juice was subjected to Castle's test, that is, incubation with muscle meat and administration of the mixture to patients with pernicious anemia, the anti-anemic activity per unit volume was preserved. These experiments require confirmation, but they render it very possible that a functional insufficiency may be present. We do not know the way in which the function of the pyloric gland organ is regulated or whether there may be a hormonal "pacemaker" for the secretion. We know that such a process occurs in the case of the pancreatic juice, where the secretin of the duodenal wall starts and maintains the pancreatic secretion after the manner of a hormone. It is therefore not very improbable that a similar mechanism may obtain in the case of the pyloric gland organ and that here also there might be a substance which influences the secretion like a hormone does, and which might, for instance, under normal conditions be a product of the stomach wall (? fundus portion) and might be absent or diminished in amount in pernicious anemia.

Finally, we must consider the possibility that *processes in the intestine* are wholly or in part responsible. Castle's hypothesis, which is still generally accepted, includes three factors: 1, A sub-

stance which is secreted by the stomach glands, namely, the gastric factor or Castle's "intrinsic factor"; 2, a substance obtained from the food, the food factor or Castle's "extrinsic factor"; and, 3, a completed substance, elaborated from these two bodies, the liver factor.

The completed substance, the liver factor, is thus produced by interaction between the two first factors. This action probably must be ascribed to the intestine, especially the small intestine. From numerous observations on the occurrence of pernicious anemia in association with diseases of the small intestine—tapeworm, multiple strictures of the small intestine, sprue—we know that the small intestine, in some way or another, must play a part in the processes which control the normal formation and absorption of the completed principle. In his latest published work (1937), Castle *et al.* maintains, on the basis of many varying incubation tests, that the essential part of the interaction between the intrinsic factor and the extrinsic factor occurs in the small intestine. It is clear that the question of the most suitable medium for the completion of these processes in the intestine, pH and other factors, thus becomes paramount; and even with a relatively well-preserved pyloric gland organ, in fact even when its function is comparatively intact, it seems possible that the achylia under certain conditions might change the milieu of the small intestine in a direction unsuitable to the course of the processes concerned.

This is hardly the place for a detailed discussion of these different possibilities, I only wish to draw attention to some of the problems for future investigation. I believe that two facts have been established: 1, That the anti-anemic factor of the stomach is produced by the pyloric gland organ; but, 2, that a histologic investigation shows that the pyloric gland organ is relatively intact in pernicious anemia. Perhaps the latter discovery renders the problem still more complicated, but, as an English colleague expressed it during a visit, "it makes it all the more fascinating."

Case Reports. Case 1.—K. M. H. A., aged 40, died Sept. 21, 1933.

Clinical diagnosis: Pernicious anemia partly compensated, myelopathy, right pneumonia, right pulmonary abscess, B. coli pyuria.

Postmortem findings: (Dept. B, No. 144) Pernicious anemia, right pneumonia, right pulmonary abscess, right pleurisy, pulmonary edema, cirrhosis of the liver, perisplenitis, left parovarian cysts.

The bone marrow of the femur was red, megaloblastic erythropoiesis was seen microscopically.

Histologic examination: The fundus exhibited severe gastritis with disappearance of the specific glandular elements, chief cells and parietal cells. The gastritis gradually decreased down to the pyloric portion, but the pyloric glands seemed relatively well preserved. Brunner's glands appeared normal.

Case 2.—M. M. P., a woman, aged 68, admitted Nov. 22, died Dec. 23, 1933.

Clinical diagnosis: Pernicious anemia.

Postmortem findings: (Dept. B, No. 186) Anemia of the organs, pul-

monary edema, chronic bronchitis, disseminated and confluent purulent bronchopneumonia, fibroid pleurisy, hydrothorax, steatosis cordis.

The bone marrow of the femur was red; megaloblastic erythropoiesis was seen microscopically.

Histologic examination: The fundus exhibited severe gastritis with pronounced interstitial changes and atypical glands with disappearance of the chief and parietal cells. The interstitial changes were less pronounced in the pyloric portion, and the pyloric glands appeared well preserved. Brunner's glands seemed normal.

CASE 3.—A. F. O., a woman, aged 69, admitted Oct. 24, died Nov. 9, 1934.

Clinical diagnosis: Pernicious anemia, myelopathy, cystopyelonephritis.

Postmortem findings: (Dept. B, 153/34) Pernicious anemia, cystopyelonephritis with calculus, acute infectious hyperplasia of the spleen, disseminated bronchopneumonia, arteriosclerosis.

The bone marrow was not described.

Histologic examination: There were pronounced interstitial and glandular changes in the fundus with disappearance of the chief and parietal cells, but only very slight interstitial changes in the pyloric portion with well-preserved glands. Brunner's glands were normal.

CASE 4.—B. K. P., a woman, aged 71, admitted Jan. 12, died Feb. 5, 1935.

Clinical diagnosis: Pernicious anemia, cystopyelitis.

Postmortem findings: (Dept. B, No. 16 d) Anemia of the organs, arteriosclerosis of the coronary arteries, pulmonary edema, chronic adhesive pleurisy, gall stones.

The bone marrow was not described.

Histologic examination: The entire fundus exhibited severe gastritis with profound changes in the glands and disappearance of the parietal and chief cells. The gastritic changes continued down into the pyloric portion, although with a diminishing tendency, and the pyloric glands seemed relatively well preserved. There was perhaps a slight indication of interstitial changes in Brunner's glands which otherwise appeared normal.

CASE 5.—E. J. L., a woman, aged 77, admitted April 18, died April 24, 1935.

Clinical diagnosis: Pernicious anemia, cystopyelitis.

Postmortem findings: (Dept. B, No. 70) Anemia of the organs, slight jaundice, right bronchopneumonia, myocardial degeneration, subendocardial hemorrhages, subendothelial hemorrhages of the renal pelvis, fibrinopurulent cystitis, granular atrophy of the kidney.

The bone marrow of the femur was red.

Histologic examination: There were severe gastritic changes in the fundus with disappearance of the chief and parietal cells. Moderate gastritic changes occurred in the pyloric region with well-preserved pyloric glands. Brunner's glands were normal.

CASE 6.—L. J. J. J., a woman, aged 64, admitted June 24, died July 4, 1935.

Clinical diagnosis: Pernicious anemia partly compensated, cancer of the stomach, B. coli pyuria, arterial hypertension, cerebral thrombosis.

Postmortem findings: (Dept. B, No. 119) Senile atrophy, anemia of the organs, gastric cirrhosis, bilateral basal bronchopneumonia, aneurysm of the left ventricle of the heart, fibrosis of the myocardium, arteriosclerosis of the coronary arteries, cirrhosis of the liver, cholelithiasis of the gall bladder.

The bone marrow of the femur was not quite so red as in fresh cases of pernicious anemia. In places, it was a little gelatinous. A scirrhous cancer, not circular, was seen in the pyloric region. It extended as far as the pyloric ring.

Histologic examination: There were severe gastritis and atrophic changes in the fundus with disappearance of the chief and parietal cells. A carcinoma was present in the pyloric region, but the part around it exhibited

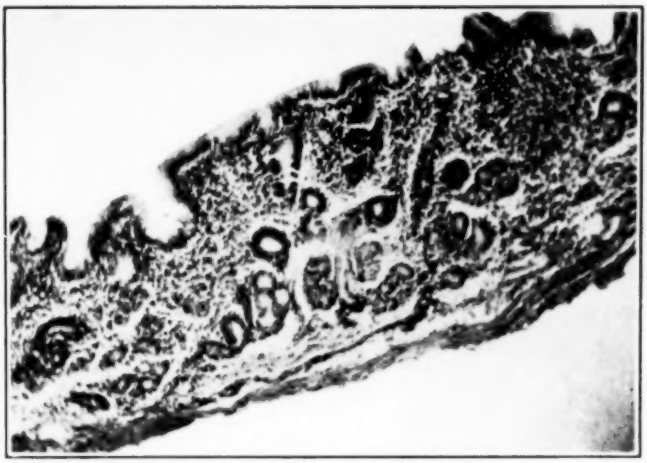

FIG. 1.—Case 7. Fundus mucous membrane. Interstitial gastritis, atrophy, deformity of glands, disappearance of chief cells and parietal cells.

FIG. 2.—Case 6. Fundus mucous membrane. Interstitial gastritis, atrophy, deformity of glands, disappearance of chief cells and parietal cells.

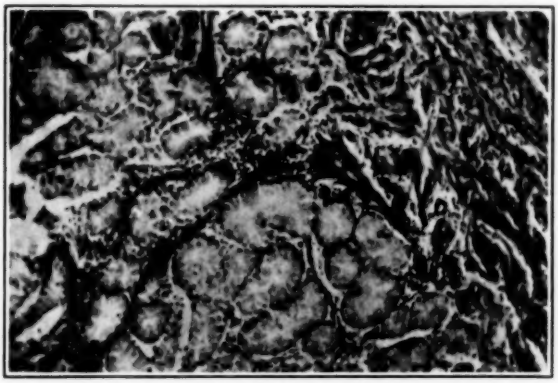

FIG. 3.—Case 2. Pylorus mucous membrane. Slight interstitial gastritis. Pylorus glands well preserved.

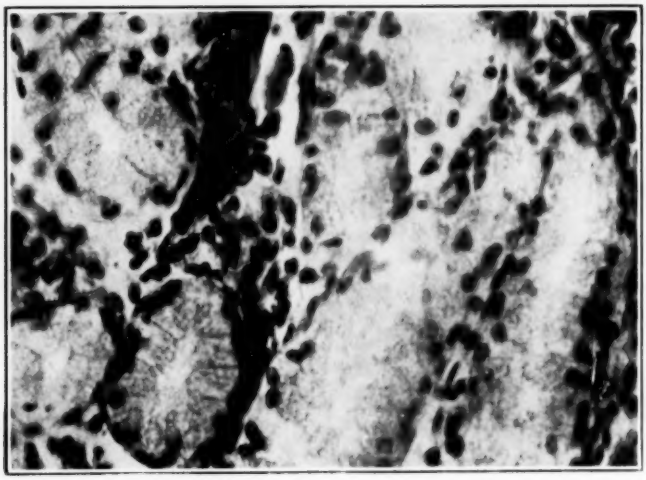

FIG. 4.—Case 2. Pylorus mucous membrane. Slight interstitial gastritis. Pylorus glands well preserved.

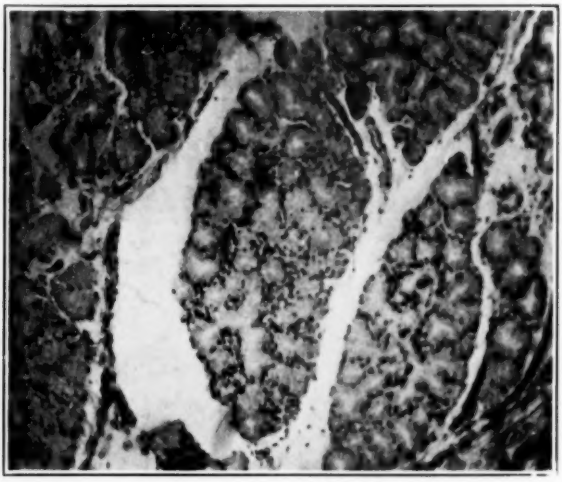

FIG. 5.—Case 2. Brunner's glands. No interstitial changes. Glands well preserved

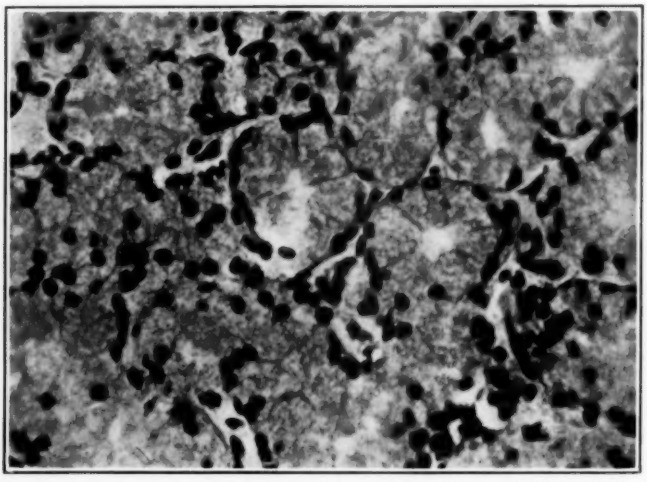

FIG. 6.—Case 2. Brunner's glands. No interstitial changes. Glands well preserved.

only slight gastritic changes in the mucosa, and well-preserved pyloric glands. Brunner's glands appeared normal.

CASE 7.—L. V. C., a woman, aged 54, admitted Aug. 16, died Aug. 19, 1935.

Clinical diagnosis: Pernicious anemia, chronic progressive polyarthritis.

Postmortem findings: (Dept. B, No. 144 d) Anemia of the organs, parenchymatous degeneration of the liver, chronic valvular endocarditis of the mitral and chord, warty endocarditis of the mitral valve, atherosclerosis of the aorta, old infarcts of the kidneys, fibroid pericarditis, ecchymoses of the myocardium, pulmonary edema.

The bone marrow of the femur was red.

Histologic examination: There were severe gastritic changes in the fundus region with atypical glands and disappearance of the parietal and chief cells, and slight changes in the pyloric region, but the glands appeared well preserved. Brunner's glands seemed normal.

CASE 8.—L. S., a man, aged 68, admitted Nov. 25, 1935, died Jan. 11, 1936.

Clinical diagnosis: Pernicious anemia partly compensated, carcinoma of the stomach.

Postmortem findings: (Dept. B, No. 4 d) Anemia of the organs, carcinoma of the stomach, bilateral confluent and disseminated bronchopneumonia, bilateral chronic fibroid adhesive pleurisy, left interstitial chronic fibroid pneumonia, aneurysm of left ventricle of heart, old infarct of myocardium, atherosclerosis of the kidneys, hypertrophy of the prostate, vesical calculus, chronic cystitis, vesica trabecularis.

The bone marrow was not described.

An ulcerated carcinoma, about 8 by 7 cm. in size, was found in the pyloric region, some distance above the pyloric ring. It was not circular.

Histologic examination: The entire fundus exhibited severe gastritic changes with altered gland structure and disappearance of the chief and parietal cells. A carcinoma was present in the pyloric region. The interstitial changes were continued down into the pyloric region. They were rather pronounced in the vicinity of the cancer, but diminished as the pylorus was approached. No definite pathologic changes could be demonstrated in Brunner's glands.

CASE 9.—A. O. P., a woman, aged 72, admitted Aug. 16, died Aug. 17, 1935.

Clinical diagnosis: Severe anemia (pernicious?).

Clinical findings: The patient was in a desperate condition when admitted and died within 24 hours. It was found that 3 years previously she was in the General Hospital for anemia. The findings then were: Ewald's test meal, ¾ hour, 60 + 42 cc. 0/16; R.B.C.: 3,800,000; neutrophils: 28%; eosinophils: 6%; basophils: 1%; monocytes: 24%; lymphocytes: 41%. She had high fever now, was unconscious, extremely anemic and subicteric. The tongue was not quite smooth and free from papillæ. Hb.: 30%; R.B.C.: 1,265,000; color index: 1.2; white cells: 11,500; platelets: 255,000; Ewald's test meal was omitted this time.

Postmortem findings: (Dept. B, No. 142 d) Anemia of the organs, senile atrophy of the organs, right disseminated bronchopneumonia, left pulmonary infarct, left chronic fibroid and adhesive pleurisy, old apical pulmonary tuberculosis, myocardial degeneration, chronic fibroid cholecystitis, calculus of the gall bladder.

In the postmortem notes the bone marrow was described as follows: "*The bone marrow of the right femur was yellow, fatty.*" Macroscopically, the liver was normal, but microscopic necrosis was demonstrated around the ventral veins, some of them being infiltrated with neutrophils. The spleen was normal macroscopically, but a considerable number of "monocytoid cells" were seen in the sinuses microscopically.

Histologic examination: The fundus exhibited severe gastritis, but the glands were relatively well preserved with distinct parietal and chief cells. The gastritic changes were less pronounced in the pyloric region and the glands seemed well preserved. Brunner's glands appeared normal.

Summary. 1. It has been shown in earlier investigations that the anti-anemic factor in the stomach (Castle's intrinsic factor) is not found in the pepsin and hydrochloric acid-producing fundus portion, but in the pyloric portion and duodenum, and that it must be secreted by the pyloric glands and the histologically identical Brunner's glands.

2. The object of the present investigation was a histologic investigation of stomach and duodenum from 8 pernicious anemia patients, with special regard to the pyloric and Brunner's glands.

3. Gastritic changes in the fundus portion with atrophy of the glands and disappearance of parietal and chief cells were found in all the 8 cases. But the gastritic changes were less pronounced in the pyloric portion, and the glands seemed relatively well preserved; no histologic changes could be demonstrated in Brunner's glands.

4. How the above finding, which at first sight is rather surprising, can be brought into line with the present conception of the pathogenesis of pernicious anemia is discussed.

* The assistance of Dr. B. Vimtrup, Director of The Pathological Department, Bispebjerg Hospital, Copenhagen, and of Dr. Tage Strunge has been of great value to me as to the provision of normal anatomic material. In microphotographing, I have been further assisted by Dr. O. Arndal, Glendale, Calif.

BIBLIOGRAPHY.

(1.) **Alsted, G.**: Klin. Wchnschr., **15**, 1229, 1936. (2.) **Bloch, C. E.**: Jahrb. f. Kinderh., **58**, Ergänzungsheft. 121, 1903. (3.) **Buechner**: Die Histologie der pept. Veraenderungen und ihrer Beziehungen zum Magencarcinom, Jena, Gustav Fischer, 1927; Die Pathogenese der pept. Veraenderungen, Ibid., 1931. (4.) **Castle, W. B., Heath, C. W., Strauss, M. B.**, and **Heinle, R. W.**: Am. J. Med. Sci., **194**, 618, 1937. (5.) **Faber, K.**: Gastritis and Its Consequences, New York, Oxford University Press, 1935. (6.) **Faber, K.**, and **Bloch, C. E.**: (*a*) Ztschr. f. klin. Med., **40**, 98, 1900; (*b*) Arch. f. Verdauungskrankh., **10**, 1, 1904. (7.) **Fenwick, S.**: Lancet, **2**, 78, 1870. (8.) **Goldhamer, S. M.**: Am. J. Med. Sci., **193**, 23, 1937. (9.) **Gram, C.**: Ugesk. f. læger, **98**, 766, 1936. (10.) **Groen, J.**: Klinisch en experimenteel onderzoek over anaemia perniciosa en voorwaardelijke deficientie, Akad. prœfschr., Amsterdam, Scheltoma & Holtkema, 1935. (11.) **Gutzeit, K.**, and **Hermann, J.**: München. med. Wchnschr., **78**, 266, 1931. (12.) **Henning, N.**, and **Brugsch, H.**: Deutsch. med. Wchnschr., **57**, 757, 1931. (13) **Henning, N.**, and **Stieger, G.**: Klin. Wchnschr., **9**, 2145, 1931. (14.) **Lange, G.**: Studier over den kroniske Gastritis, København, J. Lund, 1910. (15.) **Magnus, H. A.**, and **Ungley, C. C.**: Lancet, **2**, 420, 1938. (16.) **Meulengracht, E.**: (*a*) Acta med. Scand., **82**, 352, 1934; also Ugesk. læger, **96**, 179, 1934; (*b*) Acta med. Scand., **85**, 50, 1935; also Ugesk. f. læger, **97**, 349, 1935; (*c*) Acta med. Scand., **85**, 79, 1935; also Ugesk. f. læger, **97**, 725, 1935; (*d*) Proc. Roy. Soc. Med., **28**, 841, 1935; (*e*) Ztschr. f. klin. Med., **130**, 468, 1936. (*f*) Med. Welt, **12**, 132, 1938. (17.) **Meulengracht, E.**, and **Schiødt, E.**: Acta. med. Scand., **82**, 375, 1934; also Ugesk. f. læger, **96**, 187, 1934. (18.) **Meulengracht, E.**, and **Søeborg Ohlsen, A.**: Acta med. Scand., **82**, 384, 1934; also Ugesk. f. læger, **96**, 190, 1934. (19.) **Paschkis, K.**, and **Orator, V.**: Ztschr. f. Anat. u. Entwicklungsg., **67**, 494, 1923. (20.) **Sharp, E. A., McKean, R. M.**, and **Heide, E. C. V.**: Ann. Int. Med., **4**, 1282, 1931. (21.) **Thompson, J. C.**: Ibid., **11**, 39, 1937. (22.) **Ungley, C. C.**: Lancet, **1**, 1232, 1936. (23.) **Vimtrup, B.**: Bibliot. f. Læger, **121**, 119, 1929. (24.) **Wallgren, I.**: Ueber die Veränderungen des Verdauungskanals bei der perniciösen Anämie, Jena, Gustav Fischer, 1923.

A CASE OF ERYTHREMIA, GOUT AND SUBLEUKEMIC MYELOSIS.

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The relation between erythremia and leukemia, the complication of both diseases by gout and the rarity of gout in females justify a report of the occurrence, during a 5-year period, of all three conditions in 1 patient.

Case Report. E. R. (Surg. 42376, Med. 42089), at present aged 52, white, widowed, English-born housewife, entered the hospital November 17, 1932, complaining of a left abdominal mass of 6 months' duration. The family history was not contributory; there was no history of anemia, splenomegaly or gout. The past history was uneventful. Six months before admission the patient had first noted a firm, painless mass in the left abdomen, which increased in size causing tightness of the clothing. At this time menstruation ceased except for a scant 1 day flow 3 months later. For 6 months there was increasing constipation and 2 weeks before admission, slight nocturia. There was no significant weight change in the present illness.

Physical examination revealed a well-developed, fairly well-nourished, white female, mentally clear. The skin was somewhat florid. The lips, nail beds, conjunctivæ, buccal and nasal mucosæ, fingers and toes were bluish-red in color. Multiple small cutaneous telangiectases were present on the cheeks. The retinæ were deeper colored than usual, with engorged vessels. There were no retinal hemorrhages. The optic disks were normal. The lungs and heart were not remarkable. The blood pressure was 114 mm. mercury systolic and 74 mm. diastolic. The left abdomen was filled by a firm, smooth, non-tender, medially notched mass, presumably the spleen, extending slightly to the right of the midline, 17.5 cm. inferior to the xiphoid tip and 12 cm. below the left costal margin in the midclavicular line. By cystoscopic and pyelogram examinations the mass appeared to be the spleen, displacing the left kidney slightly medially. A smooth, firm, non-tender liver edge was palpated 2 cm. below the xiphoid tip. There was no lymphadenopathy. The superficial veins of the left leg were thrombosed. Roentgen-ray examination of the extremities showed no bone or joint abnormalities. The fingers and toes were not clubbed. Pelvic, rectal and neurologic examinations were normal.

Laboratory Studies. The urine sediment was normal, and the specific gravity ranged to 1.024. The phenolsulphonephthalein test gave an excretion of 90% in 2 hours and 10 minutes in 200 cc. of urine. The stool examination was negative. Gastric analysis, using the Ewald test meal, showed no free hydrochloric acid and total acidity ranging to 7 degrees of 0.1 normal sodium hydroxide in fractional specimens. The basal metabolic rate was +12% (DuBois standards). The vital capacity was 2.8 liters.

The Wassermann and Hinton blood reactions were negative. Carbon dioxide combining power (Van Slyke) was 53.8 vol. %. Blood urea nitrogen was 11 mg. % Clotting time by the 6-tube method was 7 minutes (normal range 8 to 12 minutes); bleeding time (Duke's method) 2½ minutes; clot retraction normal. The blood platelet count was 600,000 per c.mm.

(normal). The hematocrit showed 50.6% cells, and individual cell volume 6.6 times 10^{-11} cc. A second determination (December 9) revealed 45.8% cells, and individual cell volume 6.8 times 10^{-11} cc. Icterus index was 9. Fragility test: patient's cells showed initial hemolysis in 0.46% NaCl, complete in 0.32% (normal controls showed initial hemolysis in 0.44%, complete in 0.34%).

Table 1 shows studies of the blood counts and smears.

TABLE 1.—BLOOD COUNTS AND BLOOD SMEARS IN A CASE OF ERYTHREMIA AND SUBLEUKEMIC MYELOSIS.

Date.	Hemoglobin, % (Sahli).	Erythrocytes, millions per c.mm.	Leukocytes, thousands per c.mm.	Neutrophils, %.	Lymphocytes, %.	Monocytes, %.	Eosinophils, %.	Basophils, %.	Immature leukocytes, %.	Erythrocytes.
1932.										
Nov. 17	105	7.08	11.1	77	17	2	0	1	Unclassified, 3	Anisocytosis, poikilocytosis, occasional microcytes, occasional normoblasts; reticulocytes, 1.2%.
19	117	7.60								
20	16.15*	7.48	12.0	79	15	2	2	0		
21	..	7.39	12.3	81	11	3	2	0		
22	..	7.56	12.7	88	6	1	1	3		
26	16.04*	7.25	13.2							
28	105	7.66	18.5	86	6	1	3	3	Myelocytes, 2	Reticulocytes, 2.7%.
29	106	6.91	8.2							
30	..	..	..	82	11	1	5	1	...	Moderate achromia and anisocytosis.
Dec. 4	95	5.89	10.4							
9	116†	6.73	5.8							
10	102	6.24								
16	98	5.73	3.0							
17	..	..	3.1	72	22	1	4	1	...	As above; slight polychromatophilia.
1938.										
Jan. 15	60‡	3.60	7.5	76	18	2	2	2	Numerous band forms; myelocytes, 2	As above.
Apr. 2	70	3.70	7.2	76	15	4	3	2	Band forms, 30	As above; occasional tailed forms.
6	70	3.80	5.8	78	16	4	2	0	Myeloblast, 1	Reticulocytes, 0.9%.
14	60	3.60	6.8	...	...	...	...	...	...	As above.
18	70	3.65	4.9	76	12	6	0	0	Myelocytes, 6	As above; 1 nucleated red cell seen.

* Grams of hemoglobin per 100 cc. whole blood.
† Venous blood.
‡ Tallqvist method.

Clinical Course. On November 28, 1932, the patient was transferred from the surgical to the medical service for study and further treatment. On December 3, administration of Fowler's solution was started, 3 minims t.i.d., increasing 1 minim t.i.d., until the patient received 9 minims t.i.d. On December 12, puffiness of the eyelids, coryza, lacrimation, frontal headache, nausea and vomiting appeared, and medication was stopped for 1 day, then resumed at 6 minims t.i.d. with prompt disappearance of the above symptoms. The course was afebrile. The patient was discharged December 17, 1932, with the diagnosis of erythremia (polycythemia vera). During hospitalization the hemoglobin decreased from 105 to 98% (Sahli); the erythrocytes from 7,660,000 to 5,730,000 per c.mm.; the leukocytes to 3100; the constipation, nocturia and florid complexion disappeared, and the patient was less conscious of her abdominal mass, although the latter had not appreciably changed in size or consistency. Fowler's solution,

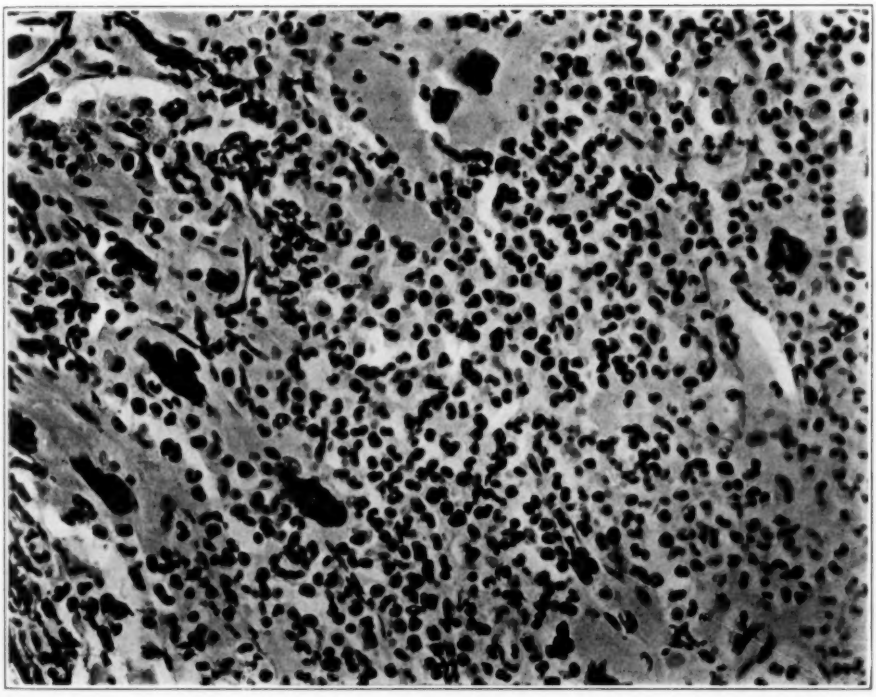

FIG. 1.—Bone-marrow biopsy showing numerous megakaryocytes and a preponderance of myeloid over erythroblastic elements. Note granulated eosinophilic myelocytes, especially in upper left corner. (× 300.)

6 minims t.i.d., was taken for 2 weeks after discharge and then stopped. Following this, no medication was taken at any time.

The patient was not seen again until January, 1938, when she consulted the outpatient department. In April, 1937, she had visited another hospital for treatment of a small skin lesion on the tip of the nose, present continuously the past year, intermittently for 14 years. An epidermoid carcinoma of the skin of the nose was diagnosed. Following local Roentgen-ray therapy, the lesion rapidly healed without recurrence.

The patient thought herself to be in excellent health until July, 1937, when a painful, red swelling, which gradually increased in size and was most noticeable when the patient had been on her feet several hours, appeared on the medial aspect of the left leg. Occasionally, momentary sharp pain was noted to shoot from this region to the left abdomen. The patient thought her spleen had become firmer and possibly slightly smaller. She gave a history of two attacks of exquisitely tender, red swelling of a big toe, lasting several weeks; the right in the spring of 1936, the left in March, 1937. The patient herself diagnosed these attacks as "gout", but took no treatment. In January, 1938, physical examination in the outpatient department revealed pallor, splenomegaly and a painful red mass, 3 cm. in diameter, surrounded by indurated varicosities, on the medial side of the left leg. Anemia was present and the blood smear showed immature granulocytes (Table 1). Admission to the hospital was advised; but the patient preferred to wait until April 2, 1938, when she entered the medical service complaining of painful swelling of the left leg of 9 months' duration. During the 5-year interval there had been no significant weight change.

Physical examination on the second admission showed normal color of the lips, nail beds and retinæ. The skin, gums and conjunctivæ were slightly pale. The retinal vessels were not distended. The spleen was very firm, not tender and apparently the same size as previously described. The liver edge was palpable as before. Lymphadenopathy was absent. Bilateral saphenous varicosities extended to the thighs, more marked on the left. A red, elevated, slightly tender, circumscribed mass, 6 cm. in diameter, was present on the medial aspect of the midportion of the left leg. Several large, firm varicose veins radiated superiorly from this mass, which was indurated, apparently subcutaneous, not attached to bone, and surrounded by a moderate degree of venous congestion. Roentgen-ray examination of the left leg showed dilated tortuous veins, apparently subcutaneous, in the upper half. The bones appeared normal except for slight loss in detail, with slightly increased density, of the upper end of the tibial diaphysis. On the lateral aspect of the midportion of the right leg was a small black eschar, 0.5 cm. in diameter, not tender or indurated. No other skin lesions were present. No tophi were found in the ear cartilages, eyelids, hands, elbows or feet. Examination otherwise was as described on the first admission.

Laboratory studies (second admission). The urine sediment showed an occasional hyaline cast in one specimen; the specific gravity ranged up to 1.026. There was no Bence-Jones proteinuria. The stool examination was negative. The basal metabolic rate was +15% (DuBois standards). The repeated blood serology was negative. Icterus index was 8. Fragility test: patient's cells showed initial hemolysis in 0.46% NaCl, normal control cells in 0.44%. Blood uric acid: April 9, 5.3 mg. %; April 19, 5.1 mg. % (normal value is less than 4 mg. %).

Table 1 shows studies of the blood counts and smears.

Clinical course (second admission). The temperature (oral) was normal except from April 8 to 10, when there was an elevation to 99.8°. At this time the patient complained of acute pain in the right great toe and stated she thought she had "gout". Examination showed redness, swelling,

warmth and marked tenderness of the first right metatarsophalangeal joint. Hyperuricemia was present. Tincture of colchicum (4 cc. t.i.d.) was administered, and considerable relief of pain and tenderness occurred within 24 hours. A mild diarrhea was associated with the first 2 days of colchicum medication. Colchicine (0.0006 gm. t.i.d.) was substituted for tincture of colchicum from April 19 until discharge. Roentgen-ray examination of both feet (April 21) showed narrowing of the metatarsophalangeal joints of the great toes, with slight reaction in the bones. A small cystic area, similar to those seen in gout, was present at the distal end of the first phalanx of the left great toe, just beneath the articular surface. Two unsuccessful attempts were made to recover crystals of urate or calcium deposit from the mass on the medial side of the left leg.

On April 12, bone marrow biopsy was performed.* A segment of marrow, 0.5 cm. in diameter, was trephined from the midsternum at the level of the fourth rib, and fixed in Zenker's solution. On section (photomicrograph), the marrow showed almost no fat tissue, being filled with numerous myeloblasts and myelocytes. Megakaryocytes and erythropoietic cells were present in moderate numbers. The section was regarded as having the appearance typical of myelogenous leukemia.

The tender mass on the left leg gradually disappeared. No change was noted in the enlarged spleen. After relief of arthralgia, the patient was very comfortable, and on April 27, 1938, she was discharged, to be followed in the outpatient department, to continue iron therapy, and to apply a tensor leg bandage should the venous induration recur.

Comment. The association of leukemia and erythremia has been much discussed.[3–5,7] During the course of erythremia a leukemic picture may develop; less frequently, the latter may precede polycythemia, and perhaps myelogenous leukemia may exhibit an initial polycythemic phase. The statement has been made[3] that when the two conditions occur in the same patient, the case is probably leukemia rather than erythremia.

Possibly this variety in clinical pictures reflects the effect of one factor on different hematopoietic tissues. In erythremia the causative factor is unknown, but the bone marrow may exhibit hyperplasia, not alone of erythrogenic elements but of leukoblastic tissue and megakaryocytes as well. In fact, in long-continued erythremia with development of anemia very disorderly blood formation, including extramedullary hematopoiesis, may occur and be reflected in the peripheral blood picture.[5]

This "panmyelopathy" of erythremia may aid in the occasional complication of this condition by gout, if gout with leukemia is due to endogenous nuclear catabolism with subsequent hyperuricemia, as has been suggested.[2] Perhaps nuclear material from only the erythroblastic elements is a sufficient source for the increased blood uric acid.[2] Gout has been described separately with erythremia (Davis,[1] Parkes Weber,[6] and others) and leukemia (Schultz,[8] Vining and Thomson,[9] and others), but to my knowledge no report has recorded both diseases with gout in 1 patient.

* I am indebted to Dr. W. Dameshek and Dr. S. Schwartz, Beth Israel Hospital, Boston, for supervision of this procedure and for pathological studies in collaboration with the Pathological Department, Peter Bent Brigham Hospital.

In the case presented, the subsequent course may determine the proper designation; for the present, the term "subleukemic myelosis" would seem acceptable.

Summary. Erythremia, gout, anemia and the blood smear and bone marrow characteristics of subleukemic myelosis occurred in a female patient observed during a 5-year period. The significance of this course of events is briefly discussed.

REFERENCES.

(1.) **Davis, N. S. III**: J. Am. Med. Assn., **92**, 1595, 1929. (2.) **Isaacs, R.**: Arch. Int. Med., **31**, 289, 1923. (3.) **Klumpp, T. G.**, and **Hertig, A. T.**: Am. J. Med. Sci., **183**, 201, 1932. (4.) **McAlpin, K. R.**: J. Am. Med. Assn., **92**, 1825, 1929. (5.) **Minot, G. R.**, and **Buckman, T. E.**: Am. J. Med. Sci., **166**, 469, 1923. (6.) **Parkes Weber, F.**: Klin. Wchnschr., **14**, 15, 1935. (7.) **Pendergrass, E. P.**, and **Pancoast, H. K.**: Am. J. Med. Sci., **163**, 797, 1922. (8.) **Schultz, A.**: Virch. Arch. f. path. Anat., **280**, 519, 1931. (9.) **Vining, C. W.**, and **Thomson, J. G.**: Arch. Dis. Child., **9**, 277, 1934.

THE MECHANISM OF THE COMPENSATORY CHANGES IN ANEMIA, ESPECIALLY AS REGARDS BLOOD CO_2 AND pH.

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The various methods by which the body compensates for the diminishing oxygen-carrying power of blood with increasing anemia have been well worked out by many investigators. It is therefore surprising to find how little has been done to elucidate the mechanism by which CO_2 is removed from the tissues in this condition, at least in man. Increasing anemia means a diminished buffering power of blood, and therefore (unless there are compensatory measures) we would expect increasing difficulty in removing CO_2 from the tissues, *i. e.*, that the normal changes in tissue CO_2 tension would produce in the blood relatively small changes in CO_2 content and relatively great changes in pH. Barr and Peters[2] and Means *et al.*[12] have proved this by demonstrating that for CO_2 tensions above 15 to 20 mm. Hg the CO_2-dissociation curve of anemic blood is flatter (though often higher) than that for normal blood (Fig. 1). At tensions below 15 to 20 mm. Hg, however, as a glance at the figure will show, the curve must be considerably steeper, *i. e.*, the blood can take up larger volumes of CO_2 with smaller pH changes than normally.

The difficulty in removing CO_2 from the tissues by anemic blood might theoretically be compensated (*a*) by an increased volume of blood flow through the tissues, and (*b*) by such an increase in pulmonary ventilation as would reduce tissue and blood CO_2 tension

to about 15 or 20 mm. Hg, at which tension, as Figure 1 shows, we might expect normal amounts of CO_2 to be absorbed per unit change of CO_2 tension.

As regards the former, Dautrebande[5] has shown that there is little or no increase of blood flow through the tissues until the hemoglobin content of blood falls to about 40%, beyond which the cardiac output rises rapidly. As regards the latter, however, we have little information.

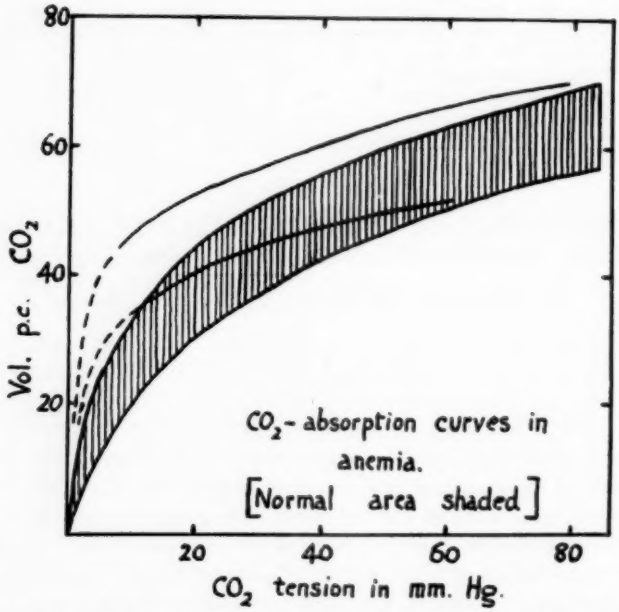

FIG. 1.—The CO_2 dissociation curves in normal and anemic bloods. The former fall in the shaded area, but the latter are higher and flatter, falling between the two higher curves. (Redrawn from Barr and Peters,[2] and Means *et al.*[12])

To elucidate the mechanism of CO_2 removal we require data concerning the CO_2 tension and pH of the tissues. To obtain this data directly in man is hardly practicable, but we can obtain indirect information concerning the state of affairs in the tissues by an examination of the venous blood, which probably gives a truer picture of conditions in the tissues than does arterial blood, on account of the fact that there is a shift of water and salts from tissues to blood in the distal portions of the capillaries, *i. e.*, into venous blood, whereas in the proximal portions of the capillaries, the shift is in the opposite direction.

The facts at present are few. It is true that some workers have investigated the blood in animals after hemorrhagic anemia, but very little has been recorded in man. Smith *et al.*[18] and Emerson

and Helmer[6] found only slight changes in the CO_2 content of venous blood and plasma in 14 and 29 cases respectively of anemia, most of which were of the pernicious type, but Peters *et al.*[15] found a definitely lower plasma CO_2 in 2 cases of secondary anemia. As regards pH, Means *et al.*[12] found a more alkaline arterial blood in 1 case each of pernicious anemia and leukemia, but a normal pH in 1 case of secondary anemia. Barr and Peters[2] also report a higher arterial pH in 2 cases of pernicious anemia but a normal pH in 1 of secondary anemia. Venous pH, however, appears to remain normal (Barr and Peters in 2 cases:[2] Peters and others[15] in 2 cases, and Emerson and Helmer[6] in 29 cases of pernicious anemia, but with a wide variation in the pH range).

On account of these meager facts and the small number of patients examined, we decided to investigate the venous blood over a wide range of hemoglobin variations.

Methods. The following estimations were made on blood drawn from the median-basilic vein, without loss of CO_2, from 75 normal students and 57 patients with secondary anemia: *a*, Red cell or hematocrit volume (Shock and Hastings[17]); *b*, blood pH (Shock and Hastings[17]); *c*, plasma or blood CO_2 content (Van Slyke); *d*, the oxygen content in some cases (Van Slyke and Neill). The hematocrit and pH values are each the average of four readings, which rarely varied more than 0.5 and 0.05 respectively. The plasma CO_2 values were made in duplicate. In some additional cases arterial blood from the brachial or femoral artery was also examined.

A few figures from cases of polycythemia are included for their comparative interest.

All subjects were either in bed, or if not, were rested for 30 minutes after arrival at the laboratory for examination.

A parallel series of observations was made on dogs 48 hours after the production of a hemorrhagic anemia or a transfusion polycythemia. In the former, the blood was centrifuged and the plasma returned to the dogs. In the latter, red cells, with a minimum of saline only, were injected.

Results. *A. Venous Plasma CO_2.* When the plasma CO_2 content is plotted against the red cell (hematocrit) content rather a wide scattering of points results. This, of course, is to be expected when we take into consideration the several influences affecting different individuals (see Discussion). When, however, we plot the average CO_2 figures for different groups arranged according to their red cell content, it is seen that increasing anemia results in a falling plasma CO_2 (Fig. 2, Curve *A*). For comparison, we have also added Curve *B*, representing the plasma CO_2 of arterial blood, calculated from figures by Shock and Hastings[17] from healthy students, and therefore of limited range. The two curves are parallel, *i. e.*, the arteriovenous difference is constant over this short range. They both show a maximum value at a hematocrit reading of 50 to 55%.

Three patients were examined on from 3 to 6 occasions during recovery from anemia. All showed a steady rise of plasma CO_2 content.

If our polycythemia cases (E, F, G, H), together with 2 others (K, L) from Peters *et al.*,[15] are at all typical, it would appear that in this condition the CO_2 curve falls again with increasing red cell content.

B. Venous Blood pH. When venous pH is plotted against red cell content, arranged as in *A*, although some scattering occurs, the average pH curve is found to fall slightly with increasing anemia and then to return to a fairly constant level of 7.34 (Fig. 2).

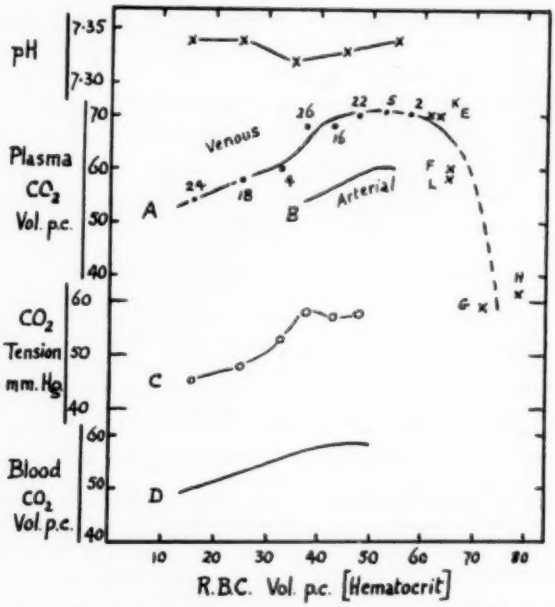

FIG. 2.—Showing the changes in pH, CO_2 content and CO_2 tension of venous plasma with increasing anemia. Each point on Curve A represents the average, and the adjacent figures the number of individuals, in each of the various groups.

C. Whole Blood, Arterial and Venous. In 17 cases, including 10 of the pernicious type, both arterial and venous bloods were also examined (Table 1 and Fig. 3). The outstanding findings are: 1, When the cases are arranged in descending order of hemoglobin or oxygen content it is found that below about 40% hemoglobin (8 cc. of oxygen per 100 cc. blood) there is a rapid fall in the arterio-venous oxygen difference (Fig. 3, *a*), which, as will be discussed later, is due to an increased blood flow through the tissues, and hence a smaller reduction of oxyhemoglobin per 100 cc. of blood. The relations of diminishing A-V oxygen difference (increasing blood flow) to A-V CO_2 difference and A-V pH difference are further shown in Figure 3, *b* and 3 *c*. 2, The average arterial pH is 7.38, which is close to that found by Shock and Hastings[17] (whose method

we used) for normal people, *viz.*, 7.39 to 7.41. Although the A-V oxygen difference bears no relation to the absolute pH values, there appears to be a relationship to the A-V pH differences, which average 0.08, a figure much greater than the normal (0.02 to 0.03). 3, Whole blood CO_2 content is not appreciably affected by anemia, although when calculated from the data in Figure 2 a small fall with increasing anemia is found (Fig. 2, Curve *D*).

TABLE 1.—ARTERIAL AND VENOUS OXYGEN, CO_2 AND pH IN 17 CASES OF ANEMIA. *Cases Given as Cc. per 100 Cc. Blood.*

Case.	Oxygen content.			Blood CO_2 content.			pH.			Type of anemia.
	Arterial.	Venous.	Difference.	Arterial.	Venous.	Difference.	Arterial.	Venous.	Difference.	
1	9.8	5.4	4.4	56.3	60.9	4.6	7.38	7.33	0.05	Pernicious.
2	*b*8.2	2.4	5.8	55.7	59.1	3.4	7.35	7.24	0.11	Pernicious.
3	8.0	2.3	5.7	49.7	54.2	4.5	7.46	7.36	0.10	Pernicious.
4	*c*7.3	3.6	3.7	68.7	69.9	1.2	7.27	7.24	0.03	Pernicious.
5	6.7	0.5	6.2	59.0	63.2	4.2	7.38	7.26	0.12	Secondary chronic.
6	6.5	2.7	3.7	41.3	45.7	4.4	..	..	..	Pernicious.
7	5.8	2.3	3.5	53.0	58.4	5.4	7.45	7.35	0.10	Cancer of colon.
8	5.5	1.9	3.6	..	..	..	..	..	..	Secondary.
9	5.4	2.3	3.1	42.4	45.2	2.8	7.39	3.34	0.05	Pernicious.
10	4.3	0.7	3.6	56.1	57.8	1.7	7.40	7.28	0.12	Pernicious.
11	*b*3.9	1.6	2.3	54.8	55.8	1.2	7.35	7.30	0.05	Pernicious.
12	*c*3.8	0.7	3.1	56.8	58.3	1.5	7.40	7.33	0.07	Pernicious.
13	3.8	1.3	2.5	..	..	..	..	..	..	Uremia.*
14	3.5	2.8	0.7	46.6	50.0	3.4	..	..	..	Secondary, chronic.
15	3.5	0.9	2.6	..	..	..	..	..	..	Pernicious.*
16	*a*2.5	0.5	2.0	..	..	..	7.38	7.28	0.10	Carcinoma, stomach.
17	*a*2.2	0.5	1.7	..	..	..	7.39	7.29	0.10	Carcinoma, stomach.

* Two cases taken from Harrop.[8]
Three cases were each examined twice. These are marked *a.a.*, *b.b.*, *c.c.*

TABLE 2.—VARIATIONS IN pH AND CO_2 CONTENT OF VENOUS BLOOD OF DOGS WITH VARIATIONS IN RED CELL CONTENT.

Hematocrit	10–20	21–40	41–60	61–76
Number of observations	11	19	11	8
Average pH	7.275	7.30	7.33	7.315
Average CO_2	49.6	50.4	49.6	54.1

D. Dogs. The results in dogs differ from those in man (Table 2). The pH curve for venous blood is lowest in severe anemia, rising to a maximum with normal red cell content. The venous CO_2 content, however, remains unchanged. These results are in keeping with those obtained after hemorrhage without anesthesia in dogs by Johnston and Wilson,[9] Bennett,[3] Milroy,[13] Evans,[7] and Riegal.[16]

Our few observations in polycythemia following transfusion in dogs indicate a falling pH and a rising CO_2 content of venous plasma.

Discussion. The CO_2 content of venous blood is at any one moment the resultant of many factors even in health, among which are metabolic rate, the ratio of pulmonary vital capacity to body weight (Apperly and Semmens[1]), external temperature (Sundstroem[19]), physical fitness (Osman and Close[14]), and so forth.

In anemia, there are other possible factors, such as altered sensitiveness of the respiratory mechanism, increased rate of blood flow, perhaps tissue tolerance, and finally failure. Consequently, in any

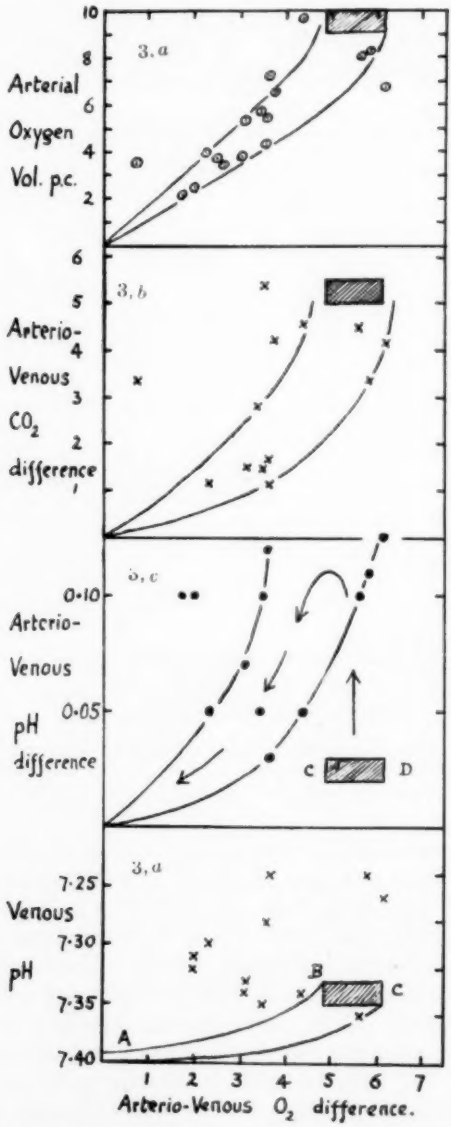

FIG. 3.—Showing the relationship of diminishing arteriovenous oxygen difference (increased blood flow through the tissues) to degree of anemia, (Fig. 3, *a*): arteriovenous CO_2 difference, (Fig. 3, *b*): arteriovenous pH difference, (Fig. 3, *c*): and venous pH, (Fig. 3, *d*). Normal ranges indicated by shaded areas.

attempt to correlate the final CO_2 content of the blood with any of these factors, considerable scattering must result. When the average of each group is taken however, as in Figure 2, the relationship of plasma CO_2 to varying red cell content of blood is clear. Further, when the CO_2 tension for each group or point on the curve is calculated from plasma CO_2 content and pH, a nearly parallel curve is obtained, indicating that with increasing anemia the CO_2 tension in the blood also falls (Fig. 2, Curve *C*).

If it be correct that the changes in venous blood are an index of tissue changes, then we also have a diminished CO_2 tension and alkali content of the tissues in anemia. This is in complete agreement with Campbell's[4] direct observations of CO_2 tension in the tissues of rabbits in posthemorrhagic anemia.

What factors are responsible for this lower tissue CO_2 tension? Certainly it is not due to a diminished CO_2 production or to oxygen want, since it is well known that the arteriovenous oxygen difference is undiminished (down to a hemoglobin level of 40 to 50%) and that metabolism remains unchanged. (Metabolism may even rise slightly owing to increased cardiac and respiratory work when the anemia becomes severe.)

When with increasing anemia there is insufficient oxygen to maintain normal tension in the tissues, a compensatory opening up of more capillaries in the tissues occurs, thereby diminishing the distance over which oxygen has to diffuse to maintain oxygen pressure (Krogh[10]). This in turn means an increase of cardiac output, which occurs when hemoglobin falls to about 40 to 50% and increases rapidly with increasing anemia (Dautrebande[5]). The increasing blood flow through the tissues means that less and less oxygen will be removed from each unit of blood, *i. e.*, with increasing anemia the arteriovenous oxygen difference diminishes (Fig. 3, *a*). This has also been shown by Harrop[8] and by Liljestrand and Senstrom.[11]

Using the diminishing arteriovenous oxygen difference as a measure of increasing blood flow, we next investigated the relationship of arteriovenous oxygen difference to arteriovenous CO_2 difference and pH difference (Fig. 3, *b* and 3, *c*). It will be seen that with increasing blood flow through the tissues (falling A-V O_2 difference) there is also a fall from the normal A-V CO_2 difference (5 to 5.4 vols. %) and a fall in the A-V pH difference, *i. e.*, the venous blood more and more resembles arterial blood. This in turn means that the venous blood CO_2 and plasma CO_2 contents steadily fall without necessarily involving any increase of pulmonary ventilation.

When, however, we similarly plot the A-V O_2 difference against venous pH we find that all pH figures fall considerably below the area A B C (Fig. 3, *d*) into which they should theoretically fall if venous pH changes were merely due to increased blood flow through

the tissues. Further, many of the A-V pH differences are considerably greater than the normal figure (0.02 to 0.03). The reasons for these differences are shown in Figure 4 in which both the arterial and venous blood CO_2 figures are plotted. The line A B represents the shift in CO_2 tension, content and pH when normal arterial blood changes to the venous condition. In the anemia cases, however, although the shift in CO_2 content is less than normal (see also Fig. 3, *b*), the shift in both CO_2 tension and pH of the group as a whole is considerably greater than normal. In other words, with increasing anemia and therefore diminishing buffering power, greater and still greater increases of CO_2 tension are necessary to make arterial blood take up its normal amount of CO_2. The H-ion concentration, therefore, must also steadily rise (see also the early pH fall in Figure 2).

This brings us back to a consideration of Figure 3, *c*. The normal A-V oxygen difference is 5 to 6 vols. % and the pH difference 0.02 to 0.03. These facts are represented by the area C D. With increasing anemia down to 40 to 50% hemoglobin there is an increasing difficulty in taking up CO_2 and consequently a rising CO_2 tension and H-ion concentration in both tissues and venous blood, with increasing A-V pH difference, although the A-V oxygen difference remains unchanged. At and below 40 to 50% hemoglobin (8 to 10 cc. oxygen %), however, there is an opening up of capillaries and an increased blood flow. The venous blood then comes increasingly to resemble arterial blood and the large A-V pH difference now falls rapidly. The rise and fall of pH difference is represented by the arrows in Figure 3, *c*. From this it would appear that rising CO_2 tension and pH difference precede the opening up and dilatation of capillaries, and suggest a causal relationship. This is supported by the figures in Case 4, which has the highest arterial and venous CO_2 and the lowest pH; *i. e.*, a CO_2 acidemia (? cause). These are accompanied by a low A-V oxygen difference and the lowest A-V CO_2 and A-V pH differences in the series, *i. e.*, one of the greatest increases in tissue blood flow. The rising H-ion concentration might also be expected to result in pulmonary hyperventilation, a fall in alveolar CO_2 tension (reported by some authors but indicated in only some of our arterial blood figures in Figure 4) and the falling plasma CO_2 content seen in Figure 2. The diminishing plasma CO_2, therefore, is due to the two factors, *viz.*, hyperventilation and increased blood flow.

One or two items among our figures are of interest:

Nearly all cases have higher arterial and venous CO_2 contents than the average normal, or at least they lie in the high normal area (Fig. 4). Although undoubtedly largely due to the relatively greater proportion of plasma (which holds more CO_2 than corpuscles) in anemic blood, there must be some other factor, since the blood CO_2 content does not vary as exactly as we would expect with the

relative volume of plasma (or inversely as the degree of anemia). These facts have also been noted by others.[2,12] The variation of the pH over a range much wider than normal has been commented upon by Emerson and Helmer,[6] although they offered no explanation thereof.

The diminution of the A-V CO_2 difference is rather more marked than normal compared with the A-V oxygen difference, giving a R.Q. (respiratory quotient) of 0.84. Many cases, indeed, have as low an R.Q. as is found in diabetic acidosis, which suggests the presence of lactic or other acid in these severe anemias. Most

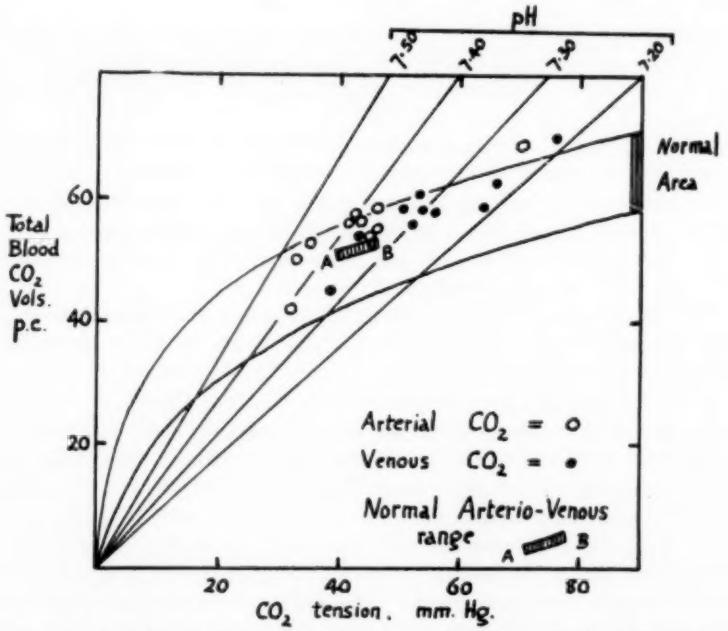

FIG. 4.—Showing the shift from arterial to venous pH, CO_2 content and CO_2 tension in 10 cases of anemia, compared with the shift in normal blood (area A B).

authors, however, deny any lowering of R.Q. in anemia, *e. g.*, in Harrop's 10 cases the R.Q. was 0.93.[8] Of course, one must also bear in mind that venous blood even normally varies widely in different veins, and we cannot assume that blood from the arm is representative of the venous blood as a whole.

In our dog experiments (Table 2) the falling pH but level plasma CO_2 curve support our general conclusion that anemia leads primarily to a rising H-ion concentration. The compensatory increase of blood flow in man, by which rising H-ion concentration and CO_2 tension are prevented from rising still higher, does not, however,

appear to occur in dogs, since the pH continues to fall in the latter and the plasma CO_2 content remains at a steady level.

As regards our few cases of polycythemia, the data are too few to allow us to arrive at any conclusion concerning the underlying mechanism, although the falling plasma CO_2 is no doubt immediately due to the obvious dyspnea seen in these patients. It is of interest to note, however, that just as Campbell[4] found a steadily diminishing CO_2 tension in the tissues of rabbits more or less parallel with the fall of hemoglobin content below normal (referred to above), so in the polycythemia following transfusion he also found a falling tissue CO_2 tension. These experiments together with our findings suggest that the same conditions are present in man.

Summary. 1. Beyond a few isolated facts there is not, so far as we know, any complete study of the relations between blood CO_2, pH and oxygen in anemia, nor of the methods by which the body rids itself of CO_2 in this condition.

2. In a group comprising anemias of various types we found, with increasing anemia, that:

A. Plasma CO_2 falls at first more rapidly and then more slowly. Whole blood CO_2, however, remains practically unchanged.

B. Venous pH falls at first but later returns to normal. Arterial pH, however, remains normal.

C. The arteriovenous oxygen, CO_2 and pH differences, though little affected until the hemoglobin falls to about 40%, thereafter fall rapidly.

3. These changes are interpreted as indicating that:

A. In the less severe anemias (down to about 40% hemoglobin) rising hydrogen-ion concentration of venous blood, brought about by diminishing buffering power of blood, leads to some hyperventilation, with fall of plasma CO_2 and restoration of arterial pH.

B. In the more severe anemias (less than about 40% hemoglobin) the earlier rise of hydrogen-ion concentration has directly or indirectly brought about a greater blood flow through the tissues, so that the differences between arterial and venous oxygen, CO_2 and pH diminish, thus lowering tissue CO_2 tension but sparing the respiratory mechanism.

4. Observations on dogs support 3*A* above, but indicate that 3*B* operates to a less extent than in man.

5. In a few cases of polycythemia, the plasma CO_2 falls rapidly with rise of red cell content.

6. In anemia, the respiratory quotient, as calculated from blood oxygen and CO_2 contents, is within normal limits.

We are indebted to Dr. W. B. Porter, Professor of Medicine, for permission to use some of the cases under his care.

REFERENCES.

(1.) **Apperly, F. L.**, and **Semmens, K. M.**: Med. J. Australia, **2**, 226, 1928. (2.) **Barr, D. P.**, and **Peters, J. P.**: J. Biol. Chem., **45**, 571, 1921. (3.) **Bennett, M. A.**:

Ibid., **69**, 675, 1926. (**4.**) **Campbell, J. A.**: J. Physiol., **65**, 255, 1928. (**5.**) **Dautrebande, L.**: Compt. rend. seances, Soc. biol., **93**, 1029, 1925. (**6.**) **Emerson, C. P.**, and **Helmar, O. M.**: Arch. Int. Med., **55**, 254, 1935. (**7.**) **Evans, C. L.**: Brit. J. Exp. Path., **2**, 105, 1921. (**8.**) **Harrop, G. A.**: J. Exp. Med., **30**, 241, 1919. (**9.**) **Johnston, C. G.**, and **Wilson, D. W.**: J. Biol. Chem., **85**, 727, 1930. (**10.**) **Krogh, A.**: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922. (**11.**) **Liljestrand, G.**, and **Senstrom, N.**: Acta Med. Scand., **63**, 130, 1925. (**12.**) **Means, J. H., Bock, A. V.**, and **Woodwell, M. N.**: J. Exp. Med., **33**, 201, 1921. (**13.**) **Milroy, T. H.**: J. Physiol., **51**, 259, 1917. (**14.**) **Osman, A. A.**, and **Close, H. G.**: Quart. J. Med., **23**, 393, 1930. (**15.**) **Peters, J. P., Bulger, H. A., Eisenman, A. J.**, and **Lee, C.**: J. Biol. Chem., **67**, 219, 1926. (**16.**) **Riegel, C.**: Ibid., **74**, 123, 1927. (**17.**) **Shock, N. W.**, and **Hastings, A. B.**: Ibid., **104**, 565, 585, 1934. (**18.**) **Smith, L. W., Means, J. H.**, and **Woodwell, M. N.**: Ibid., **45**, 245, 1920. (**19.**) **Sundstroem, E. S.**: Univ. Calif. Publ. in Physiol., **6**, 91, 1926.

THE BLOOD PLASMA ASCORBIC ACID IN PATIENTS WITH ACHLORHYDRIA (PERNICIOUS AND IRON DEFICIENCY ANEMIA).*

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A number of studies reported in the literature suggest that achlorhydria might be a predisposing factor in the cause of vitamin C deficiency. The diagnosis of hypovitaminosis-C in patients with achlorhydria has been based on: 1, symptomatology;[6,9,11,14] 2, increased capillary fragility;[3,5,15,16] 3, decreased urinary excretion of ascorbic acid following ingestion of the vitamin;[2] or, 4, a decreased ascorbic acid level in the blood.[12] In the last study, performed in Denmark, the blood ascorbic acid averaged 0.20 mg. per 100 cc. in achlorhydric patients as compared to 0.30 mg. per 100 cc. in normal individuals. These values are lower than those usually encountered in this country. In order to obtain further information on this problem, we determined the reduced ascorbic acid of blood plasma in a group of patients with achlorhydria associated with pernicious or iron deficiency anemia. The results in general seem to confirm the hypothesis that a relationship exists between achlorhydria and vitamin C deficiency.

Procedure. The subjects consisted of 44 clinic patients on whom a diagnosis of pernicious or iron deficiency anemia had been made previously. The presence of complete achlorhydria had been established in practically all cases by the histamine fractional gastric analysis (exceptions noted in

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TABLE 1.—BLOOD PLASMA ASCORBIC ACID VALUES IN NORMAL INDIVIDUALS AND IN PATIENTS WITH ACHLORHYDRIA.

Normals.				Pernicious anemia.						Iron deficiency anemia.					
Name.	Age.	Sex.	Ascorbic acid, mg. per 100 cc. plasma.	Name.	Age.	Sex.	R.B.C., mil. per c.mm.§	Hgb., gm. per 100 cc.	Ascorbic acid, mg. per 100 cc. plasma.	Name.	Age.	Sex.	R.B.C., mil. per c.mm.§	Hgb., gm. per 100 cc.	Ascorbic acid, mg. per 100 cc. plasma.
Adequate Intake of Vitamin C.															
A. S.	63	F	1.08	S. P.*	67	F	5.24	15.7	0.52	L. B.†	43	F	5.11	15.3	0.44
L. F.	50	F	0.84	G. J.	45	M	5.12	16.6	0.40	H. N.	42	F	5.21	15.0	0.48
M. L.	47	F	0.80	M. D.	73	F	4.85	14.9	0.56	H. B.	49	F	4.80	14.8	1.16
S. H.	47	F	1.20	G. Y.	61	F	4.72	12.5	0.51	J. S.‡	44	F	5.27	14.2	0.92
A. F.	47	F	0.72	F. W.	63	F	4.70	12.0	0.72	J. W.	43	F	4.62	14.0	0.63
E. E.	45	F	0.86	C. N.	73	M	4.60	14.4	0.40	S. N.	52	F	4.80	11.8	0.48
S. T.	40	F	1.00	M. S.	53	F	4.49	16.1	0.40	E. L.§	40	F	4.77	11.6	0.40
S. A.	53	F	0.84	E. H.	60	F	4.33	14.5	0.46	C. C.	46	F	3.92	9.0	1.11
C. H.	46	F	0.80	V. T.	42	F	4.19	13.4	0.80	K. T.	52	F	4.68	8.2	0.64
V. M.	45	F	1.00	E. R.	69	F	4.11	11.2	0.92	V. G.	21	F	3.89	7.6	0.77
F. H.	61	M	0.88	J. M.	50	F	3.91	15.4	0.64	E. K.	47	F	3.85	7.6	0.97
W. M.	59	M	0.64	J. S.	66	M	3.88	14.2	0.48						
W. R.	47	M	0.80	B. F.	69	F	3.88	12.4	0.44						
L. C.	45	M	0.68	K. K.	63	F	3.79	12.5	0.60						
J. H.	44	M	0.96	F. C.	45	F	3.76	12.3	0.52						
				A. L.	66	F	3.45	10.7	0.72						
Mean			0.87 ± 0.03						0.57 ± 0.03						0.73 ± 0.06
D/PED×			..						7.5						2.3
Inadequate Intake of Vitamin C.															
K. L.	69	F	0.53	P. C.	41	F	4.98	12.4	0.64	E. P.	32	F	4.73	14.0	0.32
E. S.	48	F	0.80	M. M.	64	F	4.87	13.3	0.52	V. L.	65	M	5.37	13.8	0.60
T. C.	63	M	0.44	J. B.	50	F	4.75	14.7	0.40	A. S.	43	F	4.94	13.4	0.56
C. T.	53	M	0.58	F. F.	43	M	4.35	15.1	0.32	M. C.	23	F	4.68	12.8	0.34
P. L.	52	M	0.48	E. S.	46	M	3.91	15.2	0.68	J. C.*	67	M	4.40	12.3	0.32
M. D.	49	M	0.82	R. S.	54	M	3.23	13.8	0.54	W. W.	41	M	5.16	12.3	0.40
J. G.	42	M	0.56	H. J.	50	M	2.78	10.5	0.40	A. G.*	46	F	5.40	12.1	0.56
V. G.	41	M	0.92	E. A.	76	M	2.30	9.0	0.24	L. C.	47	F	3.98	12.1	0.55
S. K.	48	M	0.64							J. M.	45	M	5.18	10.3	0.40
Mean			0.64 ± 0.04						0.47 ± 0.03						0.45 ± 0.03
D/PED×			..						3.4						3.8

* Ewald meal.

† – Maximum HCl = 4 units
‡ – Maximum HCl = 5 units
§ – Maximum HCl = 14 units
} Cases included in series as low values with histamine stimulation probably represent a functional achlorhydria.

× $\frac{\text{Difference of means}}{\text{Probable error of difference of means}}$ Results considered to vary significantly from normal when ratio is greater than 3.

table). The therapy and the erythrocyte counts and hemoglobins at the time of the tests were variable. Among the patients with a normal blood picture, those of the pernicious anemia group were usually receiving parenteral liver therapy, while those of the iron deficiency anemia* group were receiving or had received iron therapy. Patients with subnormal erythrocyte counts or hemoglobins had received: 1, no previous therapy; 2, no recent therapy; or, 3, inadequate recent therapy. No determinations made during active remission with liver or iron therapy are included in the table. Control observations were made on 24 clinic patients who exhibited no evidence of systemic disease. The diet of each subject was evaluated as accurately as possible and classified as being adequate or inadequate in ascorbic acid. Less than 30 mg. per day were regarded as inadequate. Determinations of the reduced ascorbic acid were made on blood plasma by the micromethod of Farmer and Abt.[4] Blood specimens were drawn 3 to 4 hours after a breakfast or lunch that contained no citrus fruit. Normally, the ingestion of moderate amounts of vitamin C in a meal has little effect on the plasma level after this interval of time. This is shown by the following observations. The fasting plasma ascorbic acid was determined in 6 normal individuals and a breakfast including 150 to 200 cc. orange juice (75–100 mg. ascorbic acid) was then taken. Within 3 hours after the meal, the plasma ascorbic acid had returned to the fasting level.

Results. (See Table 1.) When the diets were adequate in vitamin C, the control group had a mean plasma ascorbic acid level of 0.87 mg. per 100 cc., which falls within the normal range (0.7–1.5 mg. per 100 cc.).[1] Patients with pernicious anemia receiving an adequate diet had a mean ascorbic acid of 0.57 mg. per 100 cc.. This decrease from the normal is statistically significant. A similar decrease was not exhibited by the patients with iron deficiency anemia. Although many low values occurred in this group, the mean value of 0.73 mg. per 100 cc. is not significantly lower than the normal. When the diets were inadequate in vitamin C, the controls had a mean plasma ascorbic acid of 0.64 mg. per 100 cc. as compared to 0.47 and 0.45 mg. per 100 cc. in the pernicious anemia and iron deficiency anemia groups, respectively. The latter values are both significantly lower than the normal.

In order to confirm the assumption that the low plasma ascorbic acid values were an index of hypovitaminosis-C, an excretory test was performed on 2 patients with pernicious anemia, both of whom had plasma ascorbic acid values of 0.56 mg. per 100 cc. Following the intravenous injection of 100 mg. ascorbic acid, a urinary excretion of 2.7 and 8.9 mg., respectively, occurred during the next 3 hours. These values fall within the range observed by Ralli *et al.*[13] in patients with vitamin C subnutrition.

The plasma ascorbic acid values in patients with pernicious and iron deficiency anemia in complete remission were comparable to the values in similar patients with decreased erythrocyte counts or hemoglobins (Table 1). Several patients studied repeatedly during

* The term iron deficiency anemia is used even though the patient has recovered from the anemia.

× Probable error of difference of means Results considered to vary significantly from normal when ratio is greater than 3.
Difference of means

early remission with liver or iron therapy showed no consistent variations in the plasma ascorbic acid level.

The results obtained suggest that achlorhydria might be a factor in decreasing the assimilation of ascorbic acid. This was especially true when the diets were inadequate, as patients with iron deficiency anemia receiving adequate diets did not have a significantly depressed mean plasma ascorbic acid. The lower ascorbic acid values observed in patients with pernicious anemia receiving adequate diets might be partially explained by factors outside of achlorhydria, *e. g.*, malabsorption.

Attempts to Explain Why Achlorhydria Might be Associated With a Decreased Assimilation of Ascorbic Acid. Vitamin C deficiency in patients with achlorhydria has been variously ascribed to: 1, increased destruction of ascorbic acid in non-acid gastric juice;[5] 2, increased destruction of the vitamin by bacteria present in the small intestine;[2] and, 3, decreased absorption of ascorbic acid due to changes in the gastro-intestinal tract.[5] An attempt has been made to gain information on the importance of the above factors.

It is known that ascorbic acid becomes increasingly labile as the alkalinity of the medium is raised. For comparative purposes 10 mg. ascorbic acid were incubated in buffer solutions of varying pH's for 3 hours. At pH 1.45, which falls in the range of normal gastric juice, 14% destruction of the vitamin occurred. At pH 7.95, which represents achlorhydric juice,[8] there was 65% destruction during the same period. Under identical conditions, ascorbic acid was incubated in specimens of normal gastric juice (pH 1.25–2.1) obtained from 13 individuals after an alcohol* or Ewald meal. The destruction of ascorbic acid during a 3-hour period was inconstant and varied from 29 to 81%. The per cent destruction in achlorhydric juice was similar to that observed in the alkaline buffer solutions. There is no apparent explanation for the difference in the destruction of ascorbic acid in acid gastric juice and that occurring in buffer solutions of the same pH.

Bacteria are plentiful in the upper small intestine and stomach of individuals with achlorhydria.[18] Cultures of *B. coli*, *Staph. albus*, *B. welchii* and enterococcus were made from the duodenal contents and feces of 2 patients with pernicious anemia. Living suspensions of the above organisms incubated with ascorbic acid for 3 hours showed no destructive action on the vitamin. Bacteria having such a destructive action have been isolated recently from the gastric contents and feces of achlorhydric patients by Kendall and Chinn.[10a,b] They have shown that the ability to destroy ascorbic acid is the property of a particular strain of organism rather than a generic characteristic.

* Alcohol *per se* had no destructive action on ascorbic acid, nor did it interfere with the determination.

The presence of malabsorption in patients with pernicious anemia and achlorhydric anemia has been demonstrated previously.[7,17] To test the rate of absorption of ascorbic acid, 10 mg. per kilo were given by mouth to 6 patients with pernicious anemia and to 6 normal individuals. Blood plasma ascorbic acid determinations were made at hourly intervals. In the normals, the plasma ascorbic acid increased to a level of 1.6 to 2.7 mg. within 2 hours. Five of the patients with pernicious anemia showed normal curves. In the sixth case, the curve was practically flat, the value not exceeding 0.6 mg. per 100 cc. It is of interest that this patient did not show a normal blood value even after continued ingestion of vitamin C in liberal quantities. These observations suggest that malabsorption of ascorbic acid was a factor in at least 1 patient with pernicious anemia.

None of the above experiments establishes a single explanation for an association of vitamin C deficiency with achlorhydria. Possibly a combination of such factors as lack of an acid gastric juice, bacterial growth, and malabsorption might be sufficient to interfere with the assimilation of ascorbic acid in the patient with achlorhydria associated with pernicious or iron deficiency anemia.

Summary. The blood plasma ascorbic acid was determined in 44 patients with achlorhydria associated with pernicious or iron deficiency anemia in remission or relapse, and in 24 controls. With diets adequate in vitamin C, the mean blood ascorbic acid was significantly decreased from the normal in the patients with pernicious anemia, but not in the iron deficiency anemia group. With diets inadequate in vitamin C, the plasma ascorbic acid was significantly decreased from the controls in both the pernicious and iron deficiency anemia groups. The plasma ascorbic acid values showed no correlation with the erythrocyte counts and hemoglobins. Experiments were performed in an attempt to explain why there might be an association between vitamin C deficiency and achlorhydria.

REFERENCES.

(1.) **Abt, A. F., Farmer, C. J.,** and **Epstein, I. M.**: J. Pediat., **8**, 1, 1936. (2.) **Einhauser, M.**: Ztschr. f. d. ges. exper. Med., **98**, 461, 1936. (3.) **Ekvall, S.**: Acta med. Scandin., Suppl., **59**, 50, 1934. (4.) **Farmer, C. J.,** and **Abt, A. F.**: Proc. Soc. Exp. Biol. and Med., **34**, 146, 1936. (5.) **Göthlin, G. F.**: Arch. f. Physiol., **61**, 225, 1931. (6.) **Hausmann, T.**: Ztschr. f. klin. Med., **93**, 346, 1922. (7.) **Heath, C. W.,** and **Fullerton, H. W.**: J. Clin. Invest., **14**, 475, 1935. (8.) **Helmer, O. M., Fouts, P. J.,** and **Zerfas, L. G.**: Ibid., **11**, 1129, 1932. (9.) **Hoff, F.**: Deutsch. med. Wchnschr., **62**, 129, 1936. (10.) **Kendall, A. I.,** and **Chinn, H.**: (*a*) Proc. Soc. Exp. Biol. and Med., **38**, 8, 1938; (*b*) J. Infec. Dis., **62**, 330, 1938. (11.) **Mahlo, A.**: Deutsch. med. Wchnschr., **62**, 96, 1936. (12.) **Nielsen, H. E.**: Bibliot, f. Laeger, **130**, 20, 1938. (13.) **Ralli, E. P., Friedman, G. J.,** and **Kaslow, M.**: Proc. Soc. Exp. Biol. and Med., **36**, 52, 1937. (14.) **Schroeder, H.,** and **Einhauser, M.**: Münch. Med. Wchnschr., **83**, 923, 1936. (15.) **Schultzer, P.**: Acta med. Scandin., **81**, 113, 1934. (16.) **Schultzer, P.,** and **Griis, O.**: Ibid., **85**, 563, 1935. (17.) **Singer, K.,** and **Wechsler, L.**: Wien. klin. Wchnschr., **47**, 77, 1934. (18.) **Topley, W. W. C.,** and **Wilson, G. S.**: The Principles of Bacteriology and Immunity, 2d ed., Baltimore, William Wood & Co., p. 1544, 1936.

FATAL BACTERIAL ENDOCARDITIS DUE TO SALMONELLA SUIPESTIFER.

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In recent years it has become apparent that *Salmonella suipestifer* is a not infrequent pathogenic organism for man. The literature on human infection has been comprehensively reviewed by Harvey.[7] Although localized lesions in various organs have been described, no well-authenticated cases of bacterial endocarditis have been reported. This paper presents 2 such cases.

The organism belongs to the colon-typhoid group, and can be differentiated from *S. paratyphoid B* by its failure to ferment arabinose, trehalose, and inosite. By fermentation reactions and serologic studies *S. suipestifer* may be divided into two types, the American and the European. The European type differs from the American in forming hydrogen sulphide on lead acetate medium. Andrewes and Neave[1] showed that the American type (diphasic type or Group I) contains two types of antigen: one, non-specific and common to both types; the other, specific for the American type. Organisms of the European type (monophasic type or Group II) contain only the non-specific antigen.

The diagnosis of suipestifer infection in man is usually made by culture of the organism from either the blood stream or a local inflammatory lesion. Though readily identified by complete cultural studies, it may be mistakenly identified as *S. paratyphoid B*, if fermentations are done with only a small number of sugars. It seems highly probable that if each organism isolated as *S. paratyphoid B* were tested for the fermentation of arabinose, trehalose, and inosite, some of these would be shown to be *S. suipestifer*. As the antigenic properties of these two organisms overlap, and *S. suipestifer* may be agglutinated by *S. paratyphoid B* antiserum, this test is unreliable for identification purposes. As a diagnostic measure in cases of *S. suipestifer* infection where the organism is not recovered by culture, the demonstration of agglutinins in the patient's serum is of some value; particularly if a rising agglutination titer is found during the period of observation.

In man two separate and distinct types of infection by this organism have been encountered: first, acute outbreaks of food poisoning with symptoms referable to the gastro-intestinal tract,[4,8,13] a type of infection which frequently occurs in epidemics and runs a rapid course of short duration with a low mortality rate; second, a febrile illness associated with invasion of the blood stream. It is

with the latter type of case that this report is concerned. Frequently the resultant picture is not unlike typhoid fever; but in numerous cases a metastatic focus is set up in a distant region of the body, the portal of entry rarely being recognized. Pyarthrosis,[9b,11,16] osteomyelitis,[9b,16] splenic abscess,[15] infected fibroids,[6] meningitis,[9a] gall bladder inflammation,[15] pneumonia,[3] and cystitis[9b] have been reported with *S. suipestifer* as the etiologic agent.

In a review of the literature the author has found no case of proven endocarditis due to this organism, although 2 cases have been reported which may possibly represent *S. suipestifer* endocarditis.[5,14] In the Cincinnati General Hospital during a period of several months 2 cases of bacterial endocarditis were observed in which there is good evidence that *S. suipestifer* was the causative agent. It is believed that these cases should be reported in some detail.

Case Reports. Case 1. Hosp. No. 81519. P. L., a 47-year-old colored male, entered the medical service October 27, 1937, complaining of generalized weakness and shortness of breath of 10 days' duration. His general health had always been good. There was no history of rheumatic fever, chorea, frequent upper respiratory infections, or syphilis. While at work 10 days before entry, he suddenly became weak and short of breath and from then on remained at home because of weakness and sweats, suffering a dull discomfort in his epigastrium and vomiting several times daily. There were no chills, diarrhea, or urinary symptoms. On the day of entry he had a transient period of unconsciousness lasting several minutes. He has received no medication. Physical examination revealed a well-developed and well-nourished colored male. The temperature was 100° F., pulse rate 64 per minute, and respiratory rate 26 per minute. The pupils were round, regular, and equal, but reacted poorly to light and during accommodation. The neck veins were moderately engorged and exhibited regular pulsations about twice as frequent as the arterial pulse. The lungs were clear. The heart was enlarged to percussion and the transverse dullness in the 2d interspace was 7 cm. The heart sounds were loud, of good quality, and A2 was greater than P2. A soft systolic murmur was heard within the apex and several observers heard also a soft, blowing, early diastolic murmur along the left sternal border. The rhythm was regular. The sounds associated with auricular contraction were not heard. The radial pulses were equal, synchronous, and of Corrigan quality. The blood pressure was 180/60 mm. of Hg. The liver edge was felt 3 cm. below the costal margin. The spleen was not palpated. An old scar about 5 mm. in diameter was present on the upper portion of the glans penis. Vibratory perception in the left leg was impaired and movements of coördination poorly performed.

The erythrocytes numbered 5,020,000 per c.mm. and the leukocytes 11,400. The hemoglobin content of the blood was 14.2 gm. per 100 cc. The differential leukocyte count showed 85% neutrophils, 12% lymphocytes, 2% monocytes, and 1% eosinophils. The urine contained a trace of albumin, an occasional leukocyte, and had a specific gravity of 1.031. The blood Kahn test was 2+. A lumbar puncture showed clear, colorless fluid with 18 lymphocytes per c.mm. and a protein content of 28 mg. %. The spinal fluid Wassermann test was 3+, and the colloidal gold curve 555531000. The electrocardiogram on entry showed complete heart block.

On the ward, the patient ran a febrile course. The systolic murmur became much louder and could be heard over the entire precordium but

was not transmitted to the neck. No petechiæ or embolic phenomena were noted. The leukocyte count rose to a peak of 33,400 per c.mm. Three blood cultures taken on the 3d and 4th days after admission were positive for *S. suipestifer*. On the 4th day the cardiac rhythm changed from complete heart block to sinus mechanism with partial heart block. The *P–R* interval was 0.40 second. Six days after entry the patient's condition appeared about the same except that large numbers of pus cells appeared in the urine. Suddenly, late in the afternoon of the 6th hospital day, he became extremely apprehensive, the pulse varied from 70 to 120, and he died within 5 minutes.

The *clinical diagnoses* were: septicemia due to *S. suipestifer* with probable acute bacterial endocarditis of the mitral valve, syphilitic heart disease with aortitis and aortic regurgitation, complete heart block, and central nervous system syphilis of the paretic type.

Necropsy (19 hours postmortem, by Dr. Ritterhoff). The heart weighed 840 gm. and was moderately dilated in all its chambers. The right ventricle was 4 mm. thick; the left, 17 mm. A reddish-yellow, granular, friable vegetation approximately 1 cm. in diameter was encountered on the mural endocardium of the right atrium just above the posterior tricuspid leaflet (Fig. 1). The vegetation was surrounded by an inflammatory reaction which extended into the atrial and ventricular musculature and was continuous with another vegetation on the endocardial surface of the left ventricle just inferior to the posterior cusp of the aortic valve. A small patent sinus was found to connect the two vegetations. Neither the tricuspid nor the aortic valve leaflet was involved by the inflammatory process. Sections through the inflammatory reaction selected to include both vegetations and the septal tissue between, showed extensive acute suppuration with piling up of thrombi at each end of the sinus tract. Many clusters of Gram-negative bacilli were seen throughout the inflammatory process and a culture from one of the vegetations revealed *S. suipestifer*. At the midportion of the sinus tract where it passed through the septum, the acute inflammatory reaction was surrounded by a zone of active fibroblastic and vascular endothelial proliferation heavily infiltrated with inflammatory cells, predominantly lymphocytes. This reaction extended upward and appeared to be continuous with a similar process in the media of the aorta in the region of its origin. Although *Treponemata pallida* were not demonstrated in sections prepared by the Levaditi method, the reaction was interpreted as due to syphilis. The ascending aortic arch was dilated and the intima presented extensive, fine longitudinal wrinkling and numerous yellow and pearl-grey plaques. The semilunar cusps of the aortic valve showed rolled edges and widening of the commissures. The coronary arteries were patent throughout their trunks and main divisions and their ostia were of normal caliber. The spleen weighed 350 gm. and contained several dark-red areas of infarction. The liver weighed 2750 gm. and had prominent vascular markings. The kidneys together weighed 475 gm. Thin yellowish-green pus was present in the intravesical portion of the ureters and there was marked injection about the trigone of the bladder. The brain weighed 1140 gm. and was covered by a thickened, opaque piaarachnoid.

Anatomic Diagnoses. Syphilitic aortitis with extension to the myocardium; acute ulcerative mural endocarditis; moderate coronary arteriosclerosis and myocardial fibrosis; chronic passive congestion of the viscera; chronic active perihepatitis and intrahepatic cholangeitis; acute splenitis; early acute cystitis, ureteritis, and pyelitis; cerebral gliosis, and chronic active leptomeningitis.

CASE 2. Hosp. No. 82809. D. W., a 31-year-old white male laborer, was admitted to the medical service on Nov. 24, 1937. At this time he was

too ill to give a history but subsequently it was learned that he had been confined to bed for several months at the age of 10 because of fever and migratory polyarthritis. For the past 5 years he had noted mild dyspnea on exertion. Eight weeks before entry he contracted a head cold accompanied by a non-productive cough which forced him to leave his work. From this time on he became weaker, more dyspneic, and had numerous chilly sensations and night sweats. For 6 weeks he had been conscious of his heart beating rapidly. Four weeks before entry he began to expectorate reddish-brown, sticky material and soon thereafter experienced a pleural type of pain in the left chest. At this time he noted swelling of his legs.

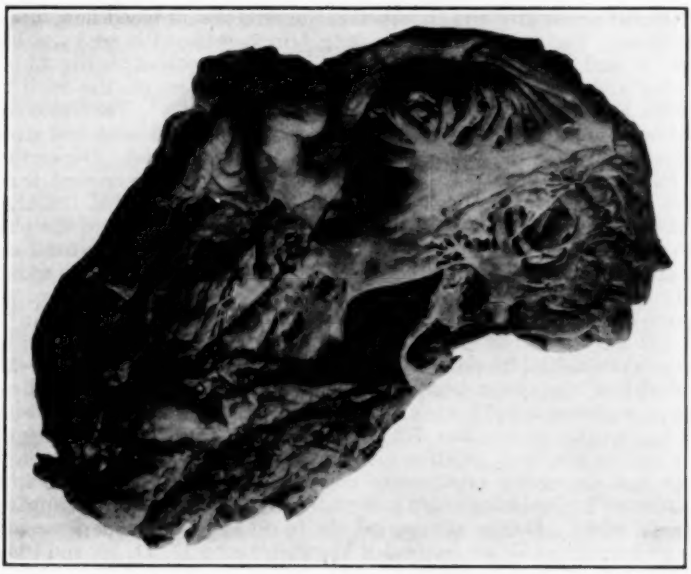

FIG. 1.—Right side of heart of Case 1; broad, tailless arrow in center of figure points to vegetative lesion superior to the posterior tricuspid leaflet. The vegetative process passes through the interventricular septum to reach the left ventricle just below the aortic valve.

On admission, the patient appeared moribund. The rectal temperature was 99.8° F., and the respiratory rate was 46 per minute. Neither the pulse nor the blood pressure could be obtained in the arms or the legs. The patient was orthopneic, cyanotic, and very restless. The thorax was symmetrical and there was evidence of partial consolidation at the base of the left lung with medium râles at the right base. The heart was enlarged both to the left and the right; sounds were of fair quality and systolic and diastolic murmurs were heard within the apex. The cardiac rhythm was totally irregular with an apical rate of 140 per minute. The liver was enlarged and tender. The spleen was not felt and there was no evidence of ascites. There was moderate edema of the lower legs. The fingers were not clubbed and no Osler's nodes were present. The entire left arm was slightly edematous and the left side of the neck and the left supraclavicular fossa somewhat swollen.

The erythrocytes numbered 5,540,000 per c.mm. and the leukocytes 16,000. The hemoglobin content of the blood was 13.4 gm. per 100 cc. The differential leukocyte count showed 78% neutrophils, 17% lymphocytes, 3% monocytes, 1% eosinophils, and 1% basophils. The urine con-

tained a trace of albumin and had a specific gravity of 1.016. The blood Kahn test was negative and the blood urea nitrogen 11 mg. %. The electrocardiogram showed a rate of 150 per minute, auricular fibrillation, right axis deviation, and changes suggesting myocardial damage.

On the ward, the patient was given ouabain intravenously, followed by digitalis by mouth; and shortly his blood pressure was obtained at 100/70 mm. of Hg, at which level it remained throughout his hospital stay. The apical rate was adequately slowed but he failed to improve. The edema of the left arm and the left side of the neck became more marked, and tender cordlike axillary and external jugular veins became palpable on this side. Within a few days superficial collateral veins were observed over the left upper arm and thorax with the direction of blood flow toward the midline. The patient had a spiking temperature with peaks as high as 105° F. and occasional chills. Icterus became apparent on his 2d hospital day and progressed thereafter; the icteric indices on the 2d, 13th, and 16th hospital days were 39, 77, and 91 respectively. The urine contained both bilirubin and urobilinogen, van den Bergh tests showed strong direct reactions, and the erythrocyte fragility test was normal. The erythrocyte count fell to 3,200,000 per c.mm. and there was a persistent leukocytosis which reached a peak of 26,000 per c.mm. Repeated urinalyses revealed no significant change from the admission specimen and the blood urea nitrogen never rose. A pleural friction rub and signs of partial consolidation appeared over the left upper lobe. The patient continued to have bloody sputum from which *S. suipestifer* was recovered on culture. On numerous occasions an early blowing diastolic murmur was heard in the third left interspace but this was by no means constant. During the last 2 weeks a pericardial friction rub was noted intermittently and for the same period of time the spleen was readily felt. Petechiæ of the skin and conjunctivæ were first noted 1 week before death. Blood cultures were positive for *S. suipestifer* on the 2nd, 7th, 8th, 9th, 13th, 15th, and 20th hospital days; one culture was negative on the 6th day. Despite the increasing icterus and decreasing erythrocyte count, large doses of sulphanilamide were started 11 days after entry and continued for 9 days without apparent beneficial effect. During this period the blood sulphanilamide concentrations as determined by the method of Marshall[10] were 17, 11, 10, and 16 mg. %. The patient died on the 21st hospital day.

The clinical diagnoses were: septicemia due to *S. suipestifer* with probable acute bacterial endocarditis of pulmonary valve, rheumatic heart disease with mitral stenosis and insufficiency, auricular fibrillation, thrombosis of left subclavian and jugular veins, multiple pulmonary infarcts, and toxic hepatitis.

Necropsy (16 hours postmortem, Dr. Ritterhoff). The pericardial cavity contained 150 cc. of dark amber fluid and the visceral and parietal surfaces of the pericardium were thickened and opaque. Over the anterior surface of the right atrium there was a yellow fibrinous area approximately 3 cm. in diameter. The heart weighed 335 gm. and all its chambers were dilated. The right ventricular wall was 3 mm. thick, the left, 12 mm. The leaflets of the mitral, tricuspid, and aortic valves were thickened and opaque. The pulmonary valve presented no abnormalities. On the auricular surface of the posterior mitral cusp there was a dark, reddish-brown, firmly adherent vegetation approximately 1 cm. in diameter. Microscopic examination of the vegetation revealed an acute inflammatory reaction composed chiefly of neutrophils enmeshed in irregular masses of fibrin. Numerous Gram-negative bacilli were present. The chordæ tendineæ of the mitral and tricuspid valves were thickened, shortened, and yellowish-white in color. The mural endocardium of the right auricular appendage contained a yellowish-red firmly adherent thrombus. The upper lobes of both lungs were consolidated throughout and several dark-red, well demarcated areas

of infarction were seen in the left. The spleen weighed 225 gm., and at the superior pole there was an infarct. The kidneys together weighed 250 gm.; the left contained several areas of infarction. The liver weighed 1565 gm., the biliary passages were patent, and the parenchyma exhibited evidence of marked passive congestion. The left subclavian and jugular veins were occluded by dark red, granular thrombi.

Anatomic Diagnoses. Chronic rheumatic pancarditis with focal epicarditis, perivascular myocardial fibrosis, fibrosis of the aortic, mitral, and tricuspid valves; right auricular thrombosis; acute ulcerative mitral endocarditis; multiple infarcts of the spleen, kidneys, and lungs with associated acute fibrino-purulent pleuritis; acute splenitis; thrombosis of the left jugular and subclavian veins; subacute cholecystitis; subacute intrahepatic pericholangeitis; marked chronic passive congestion and central zone necrosis of the liver.

Discussion. The organisms isolated by blood cultures in each case and from the vegetation in Case 1 gave the characteristic biologic reactions of *S. suipestifer*. The organisms failed to produce hydrogen sulphide on lead acetate media and were agglutinated in high dilution (1 to 1280) by an antiserum of the specific phase of the American type. The repeatedly positive cultures, coupled with the demonstration of many Gram-negative bacilli in sections of each vegetation at necropsy, constitute proof which seems adequate to establish this organism as the etiologic agent of the endocarditis. The etiologic significance of the organisms recovered from the blood stream of Case 2 is further suggested by the fact that they were agglutinated in a dilution of 1 to 160 by the patient's serum with the titer rising to 1 to 2560 during the period of hospitalization.

The clinical picture presented by these patients was that of a severe infectious process with endocarditis. As in most cases of *S. suipestifer* septicemia, no portal of entry for the infection was discovered and there was no known exposure to infected human beings or hogs. Petechiæ were never present in Case 1 and developed late in the course of the disease in Case 2. Clubbing of the fingers was not present in either case and peripheral embolic phenomena were absent. Each patient went downhill rapidly after entry to the hospital. The treatment was chiefly supportive. In Case 2, however, sufficient amounts of sulphanilamide were given to maintain the blood concentration between 10 and 17 mg. % for a period of 8 days. During this time the blood cultures remained positive and there was no symptomatic improvement.

It is worthy of note that although an absence of leukocytosis has been emphasized as an important finding in uncomplicated cases of *S. suipestifer* septicemia,[5,7] both of the cases here reported had a marked leukocytosis. The appearance of leukocytosis during the course of septicemia with this organism may be of some value in the diagnosis of endocarditis, providing there is no evidence of other localization of the infection.

It is a well known clinical observation that cardiac arrhythmias are rarely associated with bacterial endocarditis of either the acute

or subacute type. Segal[12] recently reviewed the literature on this subject and in a total of 202 cases of acute bacterial endocarditis found 5 instances of auricular fibrillation, an incidence of 2.5%. That complete heart block is an even rarer occurrence is illustrated by the fact that in Segal's own series of 84 cases of acute bacterial endocarditis not a single instance was found. Each of the cases here presented had a marked disturbance of cardiac rhythm. Case 2 exhibited auricular fibrillation for the entire 3-week period of hospitalization. Case 1 had complete heart block on entry but 4 days later the rhythm had changed to partial heart block with a P–R interval of 0.40 second. In this case the inflammatory lesion extended through the membranous portion of the septum ("undefended space"), thus invading the region of the bundle of His before its division.

Both hearts described in this report showed distinct evidence of antecedent injury. In one instance, the vegetation was implanted on a valve scarred by a rheumatic process, a common association. In the other, the aorta and aortic valve were deformed by syphilis, yet the bacterial infection became localized on the mural endocardium overlying the "undefended space."

Summary. 1. Two fatal cases of bacterial endocarditis due to *S. suipestifer* of the American type are reported with autopsy findings. Diagnosis was established by repeated blood cultures and the findings of Gram-negative bacilli in the vegetations histologically; in one instance culture of the vegetation confirmed the presence of the causative agent.

2. The clinical course of 2 cases of endocarditis due to *S. suipestifer* was not characterized by any unusual symptoms or signs with the exception of marked cardiac arrhythmia. In one instance, auricular fibrillation occurred. In the other, complete heart block changing to partial heart block was present.

3. Sulphanilamide in large doses was given to one patient without apparent beneficial effect.

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REFERENCES.

(1.) **Andrewes, F. W.,** and **Neave, S.**: Brit. J. Exp. Path., **2**, 157, 1921. (2.) **Boycott, J.,** and **McNee, J. W.**: Lancet, **2**, 741, 1936. (3.) **Bullowa, J. G. M.**: Med. Clin. North America, **12**, 691, 1928. (4.) **Clayton, E. S.,** and **Milne, V. E.**: Brit. Med. J., **2**, 684, 1930. (5.) **Gouley, B. A.,** and **Israel, S. L.**: Arch. Int. Med., **53**, 699, 1934. (6.) **Gray, L. A.**: Bull. Johns Hopkins Hosp., **59**, 231, 1936. (7.) **Harvey, A. M.**: Arch. Int. Med., **59**, 118, 1937. (8.) **Krumwiede, C., Provost, D. J.,** and **Cooper, G. M.**: J. Med. Res., **43**, 53, 1922. (9.) **Kuttner, A. G.,** and **Zepp, H. D.**: (*a*) Bull. Johns Hopkins Hosp., **51**, 373, 1932; (*b*) J. Am. Med. Assn., **101**, 269, 1933. (10.) **Marshall, E. K., Jr.**: J. Biol. Chem., **122**, 263, 1937. (11.) **Nabarro, D., White, P. B., Dyke, S. C.,** and **Scott, W. M.**: Lancet, **2**, 868, 1929. (12.) **Segal, M. S.**: Am. Heart J., **11**, 309, 1936. (13.) **Stewart, H. C.,** and **Litterer, W.**: J. Am. Med. Assn., **89**, 1584, 1927. (14.) **TenBroeck, C., Li, C. P.,** and **Yu, H.**: J. Exp. Med., **53**, 307, 1931. (15.) **Walker, I. J., Weiss, S.,** and **Nye, R. N.**: New England J. Med., **214**, 567, 1936. (16.) **Weaver, J. B.,** and **Sherwood, L.**: J. Am. Med. Assn., **105**, 1188, 1935.

THE USE OF ELECTROCARDIOGRAPHIC CHANGES CAUSED BY INDUCED ANOXEMIA AS A TEST FOR CORONARY INSUFFICIENCY.*†

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That lack of an adequate supply of oxygen to the heart will result in changes in the form of the electrocardiogram in man, was first pointed out by Greene and Gilbert in 1921.[4] Their studies, and a number which followed, employed the rebreathing of air to bring about gradually progressive anoxemia.[5,12] Other workers, notably Larsen of Copenhagen, permitted the subjects to inhale mixtures of constant, low oxygen concentration.[7] Alterations in the electrocardiogram have also been studied after exercise.[2,10,13,15] Following such procedures, slight changes have been observed in the records of normal persons. It has been inferred that more marked variations in the level of the *RS–T* junctions and in the form of the *T* waves indicate impairment of the coronary circulation. The occurrence of similar changes in graphic records taken during spontaneous attacks of anginal pain has been regarded as evidence that such pain is caused by myocardial anoxemia.[3,11]

There can be no question as to the usefulness of an objective test which makes it possible, even qualitatively, to detect coronary insufficiency. Cardiac pain, induced either by exercise or by oxygen want, has proved to be an unreliable index, partly because it represents a subjective end-point, and also because so many complex factors are concerned in its production.[8] Besides, many patients with disease of the coronary arteries do not experience pain. The chief difficulty in interpreting the significance of changes in the electrocardiogram caused by induced anoxemia has been due to the fact that these occur, in varying degree, in many persons without evidence of cardiac or other disease. The borderline between normal variation and pathologic response has not been established

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† Presented in abstract at the Meeting of the American Clinical and Climatological Association, Atlantic City, N. J., May 3, 1938.

by measurement; nor has the precordial lead been employed in any of the previous investigations. In this study, an attempt has been made to define quantitatively the limits of normal variation and to explore the possibilities of the method with respect to its clinical applicability. The work has already been briefly recorded.[9]

Technique. The *apparatus* has been described in a previous paper[8] (Fig. 1). A tank containing 10% oxygen and 90% nitrogen furnished an unvarying concentration of oxygen in the inspired air. The oxygen mixture was admitted at a rate comparable to the normal pulmonary ventilation. The bag was kept full but not distended. By the use of 2 flutter valves the mixture was inhaled during inspiration and exhaled during expiration, without rebreathing. A two-way valve at the mouthpiece enabled the observer to connect the patient to the apparatus while breathing room air and thus accurately to record the time that he was exposed to inhalation of a low oxygen mixture. A tank containing 100% oxygen was also in the circuit, so that if necessary, by turning a needle valve, anoxemia could be quickly relieved. At the end of each period of observation, the patient was permitted to breathe pure oxygen long enough to abolish cyanosis, or to relieve pain, if this occurred.

The *procedure* differed from that followed in a study of cardiac pain[8] in that the gas mixture contained 10 instead of 12% oxygen; and attention was focussed on changes occurring in the form of the electrocardiogram. A 10% oxygen mixture was used because anoxemia was induced more quickly and the changes in the electrocardiograms were more sharply defined than with 12%. There was apparently no added discomfort or hazard to the patient. Observations were made at least 2 hours after the last meal. The temperature of the room in which the test was made was kept reasonably constant at about 68° F. The patient was allowed to rest in bed for a period varying from 20 minutes to 1 hour. The procedure was explained and the patient was told that as soon as he experienced pain in the chest or arms, he should raise his hand. The mouthpiece of the gas apparatus was then inserted and the nose clamp adjusted. The patient was allowed to breathe ordinary air through the valve of the apparatus for a few minutes. The test was then started by turning the control valve, the subject being unaware of the time when this maneuver was made. The usual period of observation was 20 minutes. However, if pain was experienced the low oxygen mixture was immediately shut off and 100% oxygen was administered.

A control 4-lead electrocardiogram was made, with the apparatus in place, before beginning the test and additional curves were taken at the end of 5, 10, 15 and 20 minutes, as well as after 100% oxygen had been given for approximately 1 minute, or until cyanosis was abolished. The precordial lead employed was the one designated as IVF, according to the terminology recommended by the American Heart Association.[1] In each lead measurements were made of the level of the *RS–T* junction; *T* wave; *P–R* interval; *QRS* interval; voltage of *QRS;* and rate. These were charted on individual sheets for each test made.

Material. One hundred and twelve tests were made on 105 persons. The groups studied are shown in Table 1. The 66 normals did not have symptoms or signs of cardiac or other disease. In doubtful cases, in addition to physical examination, teleroentgenograms were made of the heart and blood counts were taken to rule out the presence of anemia. The diagnosis of coronary heart disease, in the 17 cases so designated, was based on a history of anginal pain or changes in the form of the electrocardiogram,

or both.* In the 11 cases classified as "suspected but doubtful," only pain in the chest was present. The 6 patients with previous coronary occlusion, evidenced by history, clinical course and electrocardiographic records, were relatively young (average age, 47 years). They were free from symptoms at the time the test was made. In 3 of these cases, the control electrocardiogram was normal; in 3, the *T* wave was negative in Leads I, II or IVF, or in combinations of these leads. The 5 patients with anemia showed hemoglobin values ranging from 28 to 65%; the number of red cells varied from 1,600,000 to 4,100,000 per c.mm.

TABLE 1.—GROUPS TESTED (105 INDIVIDUALS; 112 TESTS).

Normal Controls—66	
A. Medical students (aged 20 to 33 years. Average—24 yrs.)	45
B. Miscellaneous group (aged 21 to 68 yrs. Average—42 yrs.)	21
Coronary Heart Disease—34	
A. With anginal pain	17
B. Suspected but doubtful	11
C. Old coronary occlusion (diagnosis based on clinical course and previous EKG records), with normal response to test	6
Anemia—5	
Aplastic	1
Sickle cell	1
With hepatic cirrhosis	1
Hypochromic	1
Pernicious	1

Results. Significant changes occurred only in the level of the *RS–T* junctions and in the form of the *T* waves. There was no alteration in the *P–R* intervals greater than 0.02 second. The duration of *QRS* remained constant throughout. No arrhythmias occurred. Ventricular premature contractions, present in the control record in several instances, disappeared with the induction of oxygen want.

There was no correlation between acceleration in rate and alterations in form. The usual range of increase was from 15 to 30 beats per minute; the maximal range was from 2 to 52 beats. In 2 cases, the *T* waves decreased appreciably in amplitude at a time when the rate actually became slower. Although there was but little variation in rate between the first and second 10-minute periods of observation, the changes in the electrocardiograms tended to become progressively more marked.

The voltage of *QRS* often became lower in one or more leads, but the change was usually less than 4 mm. There was no ratio between variation in the amplitude of *QRS* and in that of the *T* waves.

All of the subjects became distinctly cyanotic. The level of oxygen saturation of the blood was variable, as noted in our previous studies with the inhalation of 12% oxygen;[8] but there was no direct relationship between the degree of anoxemia and the magnitude of the changes seen in the electrocardiograms. Nor did the duration of the test determine the extent of such changes. For example,

* As yet, the opportunity has not presented itself to correlate the results of the test with anatomic lesions as found at necropsy.

in certain patients complaining of pain at the end of 4 minutes, the changes, at this time, were striking. Although alterations in the records appeared quickly, they tended to regress gradually. Even after 100% oxygen had been breathed for a minute, the return to the form of the control record was usually incomplete. It seems probable that anoxemia initiates a chemical reaction in the tissues of the heart and that metabolites, which are produced locally, accumulate. There is evidence that such substances are responsible for changes in the *RS–T* segments and *T* waves in experimental cardiac asphyxia and anoxemia.[6] Whether the electrocardiogram reverts to its original contour more rapidly when the coronary circulation is intact than when it is impaired, is at present being investigated.

No serious untoward effects were observed. Unpleasant reactions occurred on 2 occasions. In a woman, aged 60, with symptoms of early cardiac insufficiency, the test was performed twice within an hour. Mild pulmonary edema occurred after the second period of anoxemia. An injection of morphine, with rest in the overnight ward, made her comfortable and she left the hospital the following morning. A second patient, a man, 56, gave a history of dyspnea as well as pain, and his electrocardiogram showed bundle branch block. After breathing 10% oxygen for 7 minutes, he developed non-productive cough, scattered râles in the lungs, and slight substernal pain. Prompt relief was afforded by the inhalation of 100% oxygen. Because of these experiences, it was decided that the test should not be performed in the presence of cardiac insufficiency; and that it should not be given to the same patient more than once within 24 hours.

Symptoms noted in normal persons were headache, a sense of heaviness in the chest, visual hallucinations and transient dizziness —each in 1 case. In 2 patients with probable cerebral arteriosclerosis, there was transitory mental confusion. Not all of those with coronary sclerosis who gave a history of anginal attacks experienced discomfort during the test. In this respect the electrocardiogram was a more delicate index of a diminished coronary reserve than was sensitiveness to cardiac pain.

On the basis of detailed measurements made of some 700 electrocardiograms, taken during 112 tests, the following tentative criteria for normal and abnormal responses have been evolved:

Normal. 1. The *RS–T* junction is not displaced more than 1 mm. in any lead.

2. The *T* waves tend to decrease in amplitude.

3. Partial or complete reversal of the direction of *T* in Lead I or Lead IVF, or both, in the absence of any *RS–T* displacement in these leads, is of uncertain significance. It was observed in 2 of 66 supposedly normal persons.

4. Partial or complete reversal of the direction of *T* in Lead II or Lead III, or both, even though associated with *RS–T* displacement

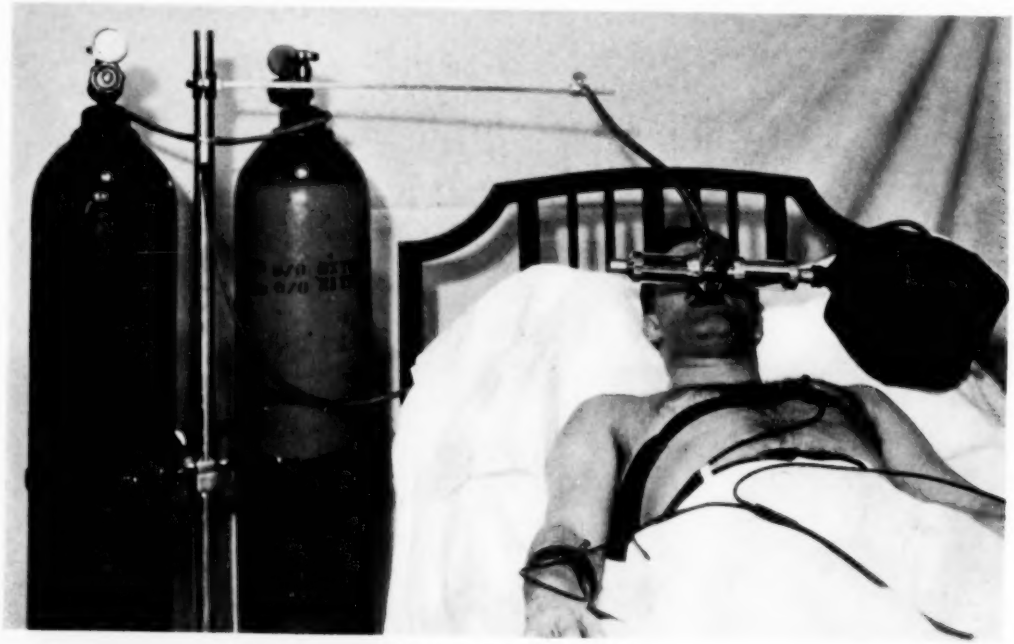


FIG. 1.—Apparatus in use.

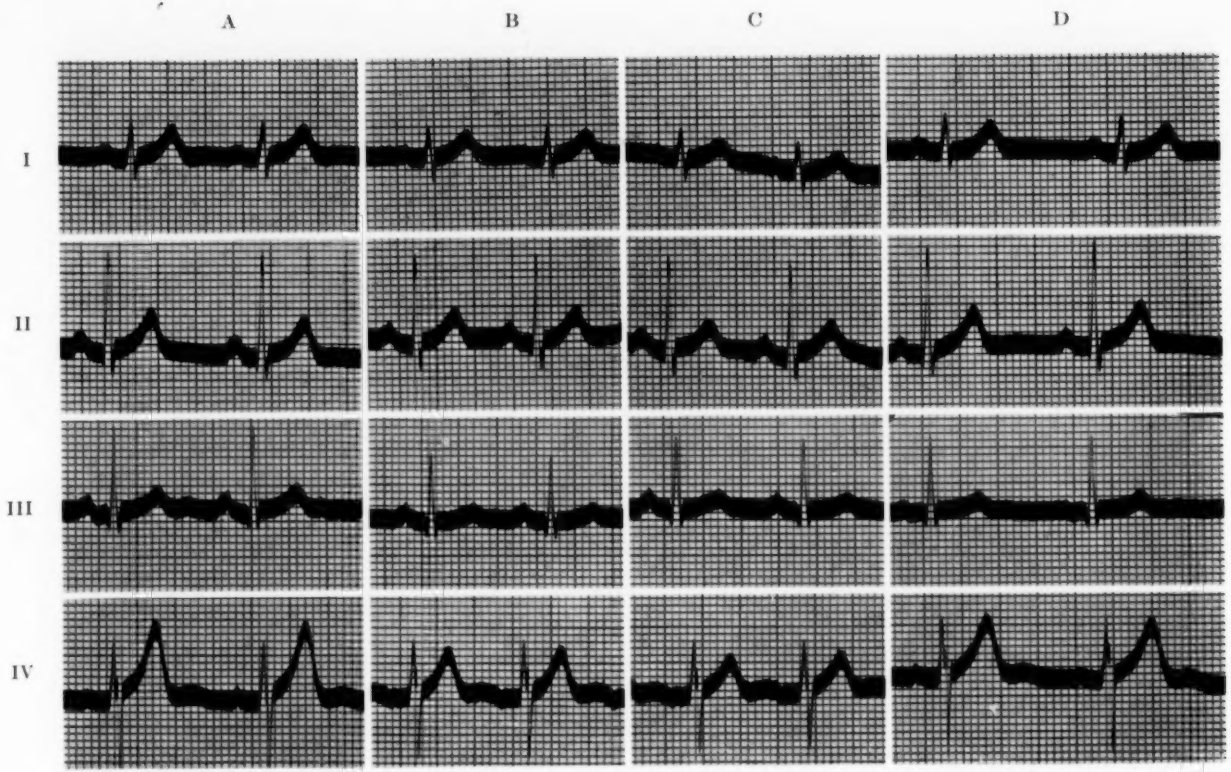


FIG. 2.—Normal, male technician, aged 29 years. *A*, control. *B*, after breathing 10% oxygen for 10 minutes. *C*, after 20 minutes. *D*, after 1 minute of 100% oxygen. In *B* and *C*, the amplitude of *T* was slightly diminished. In *D*, there was almost complete return to the form of the control.

almost complete return to the form of the control.

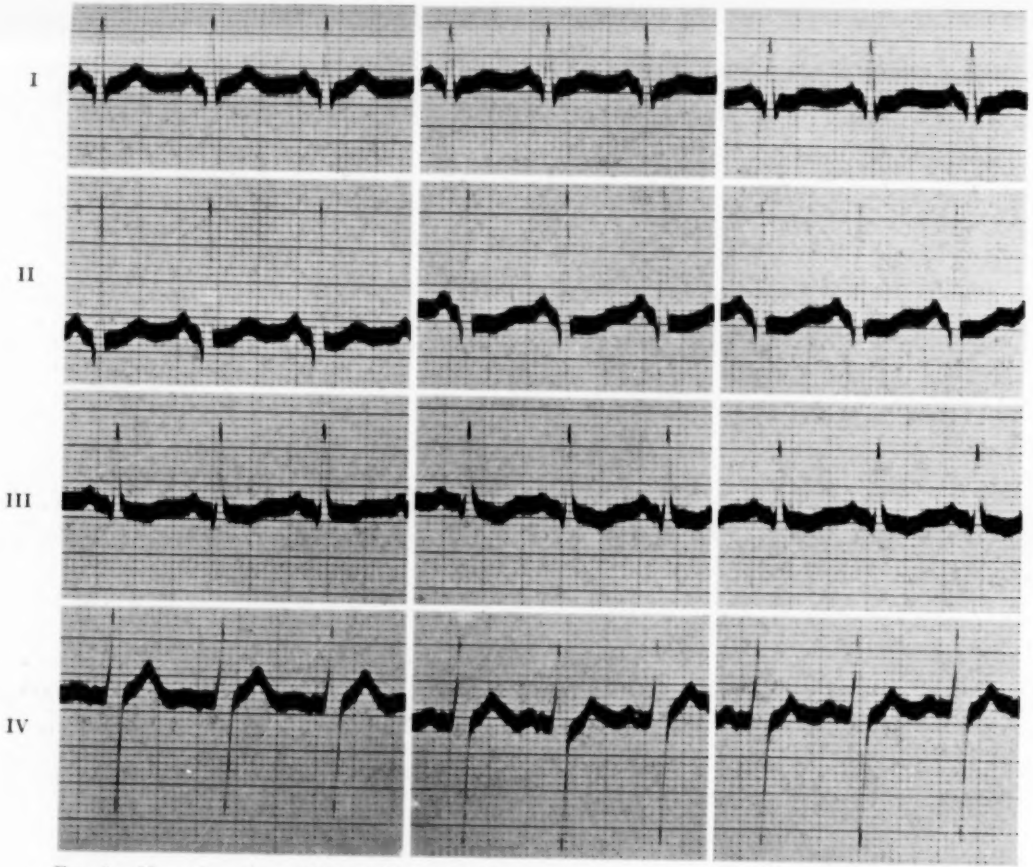


FIG. 3.—Normal, male medical student, aged 25 years. *A*, control. *B*, after 10 minutes of 10% oxygen. *C*, after 20 minutes. T_1 and T_4 became progressively lower, T_2 reversed its direction.

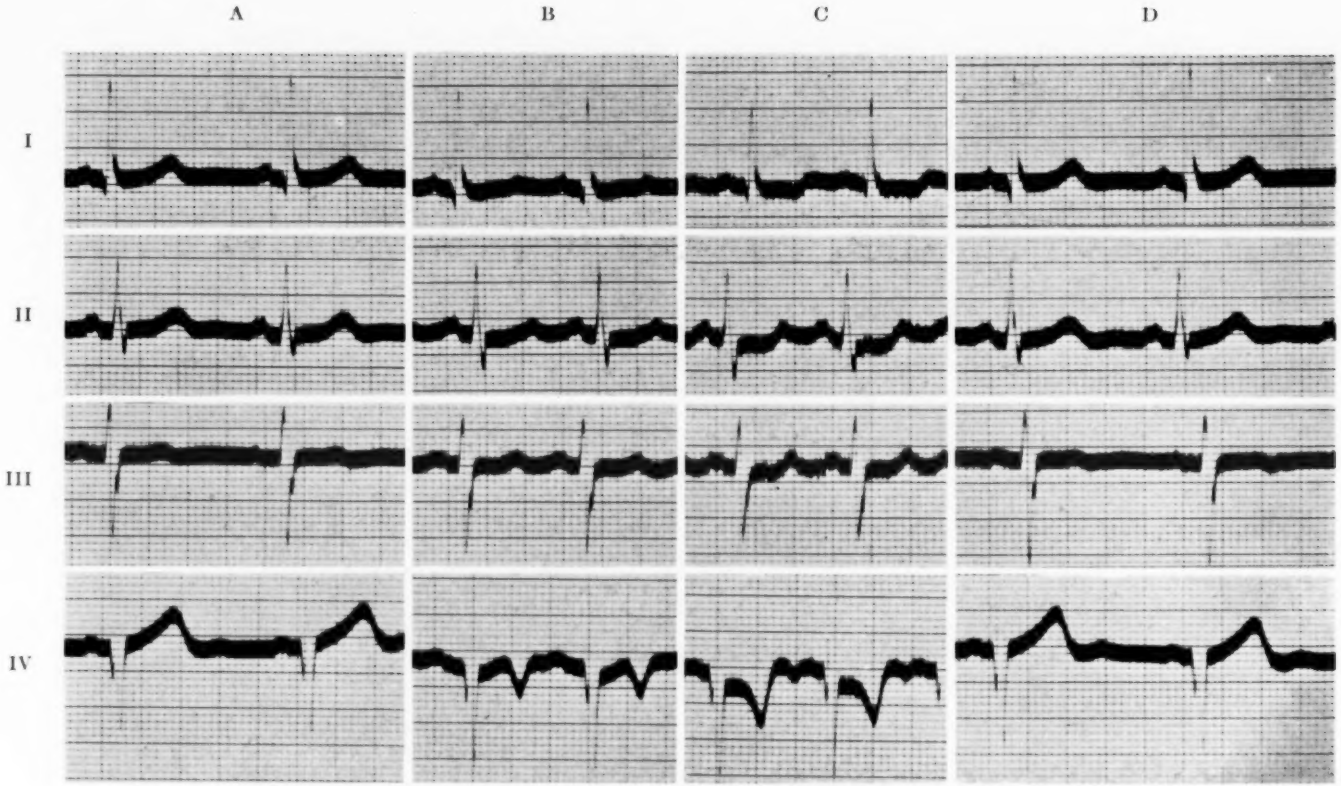


FIG. 4.—Male, aged 69 years, with coronary sclerosis and attacks of anginal pain for 5 years. Physical examination negative. *A*, control; a normal record. *B*, after 5 minutes of 10% oxygen *C*, after 8 minutes; complained of pain; test stopped. *D*, after 1 minute of 100% oxygen. T_3 and T_4 reversed their direction. *RS–T* junction depressed in all leads. In *D*, reversion to the form seen in *A*.

T_1 and T_4 reversed their direction. *RS–T* junction depressed in all leads. In *D*, reversion to the form seen in *A*.

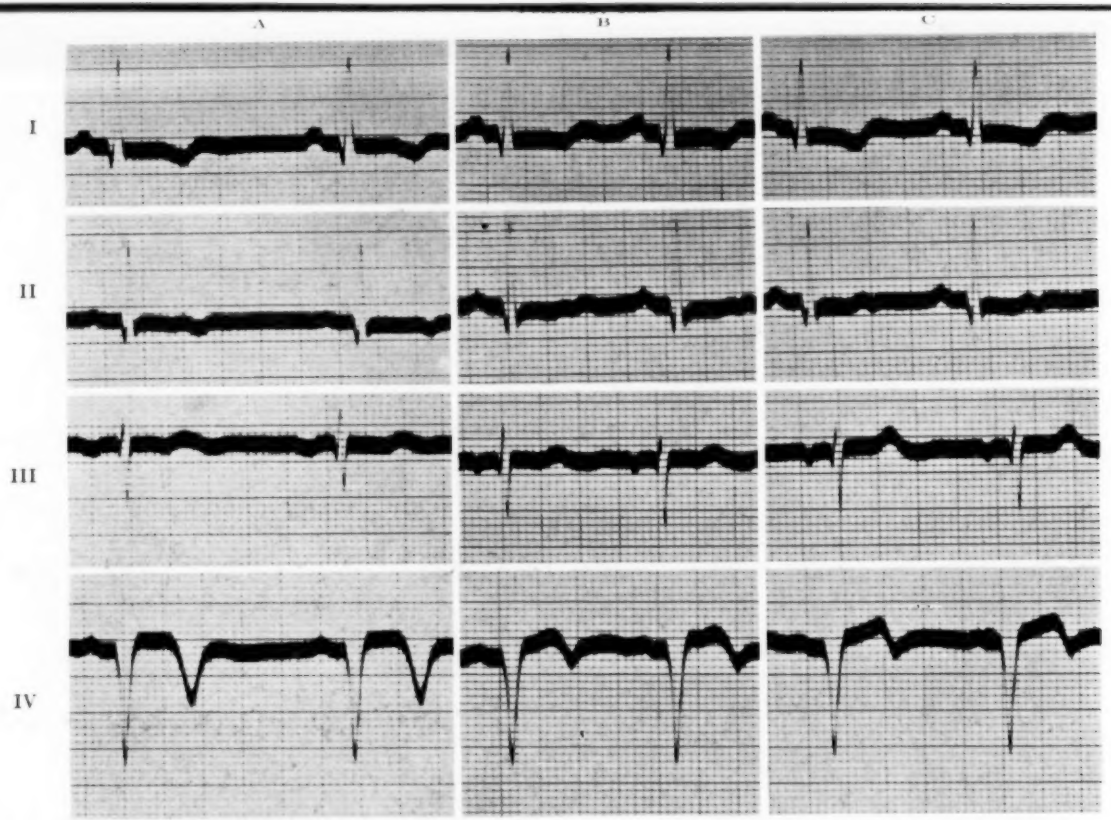
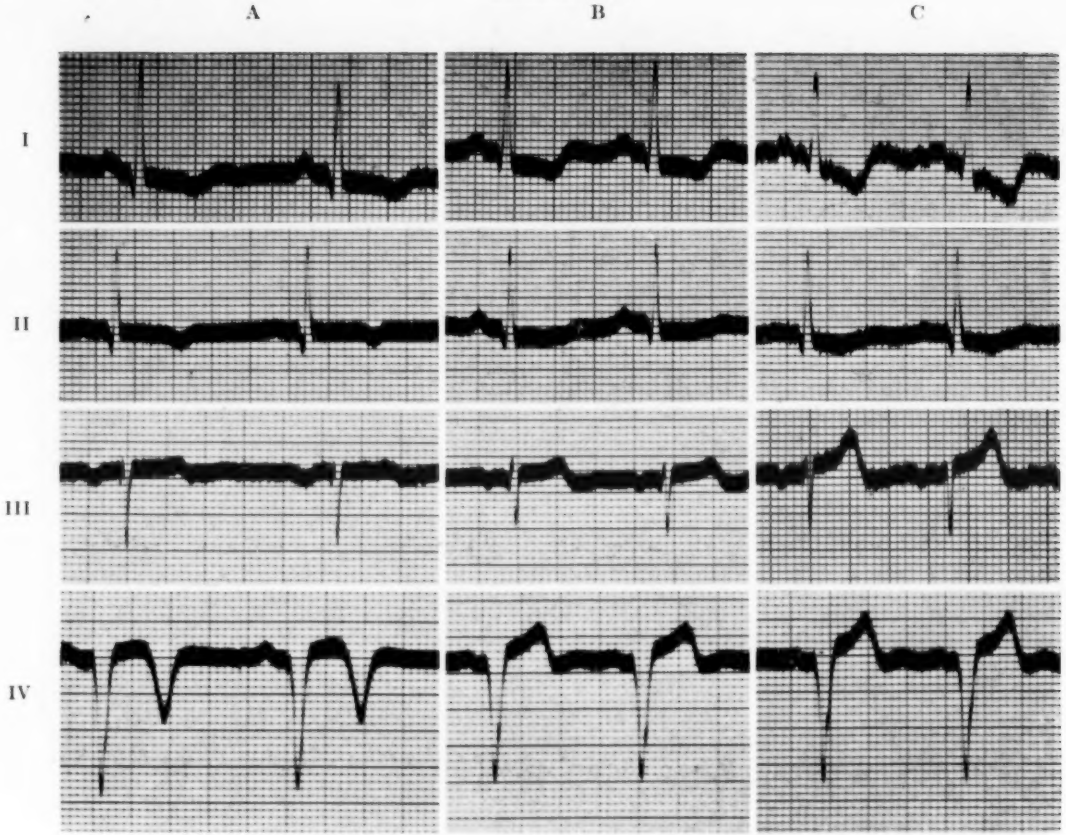


FIG. 5.—Male, aged 56 years, with coronary sclerosis. Coronary occlusion with infarction of myocardium in July, 1937. Good recovery. In December, 1937, having anginal attacks. *A*, control. *B*, after breathing 10% oxygen for 10 minutes. *C*, after 20 minutes; slight pain; felt faint. Changes in *T* and *RS–T* in all leads. T_4 completely reversed its direction. In February, 1938, clinically much improved; no anginal attacks. *A*, control. *B*, after breathing 10% oxygen for 10 minutes. *C*, after 20 minutes. No discomfort. Changes less marked in all leads. T_4 only partly reversed its direction.



A
B
C

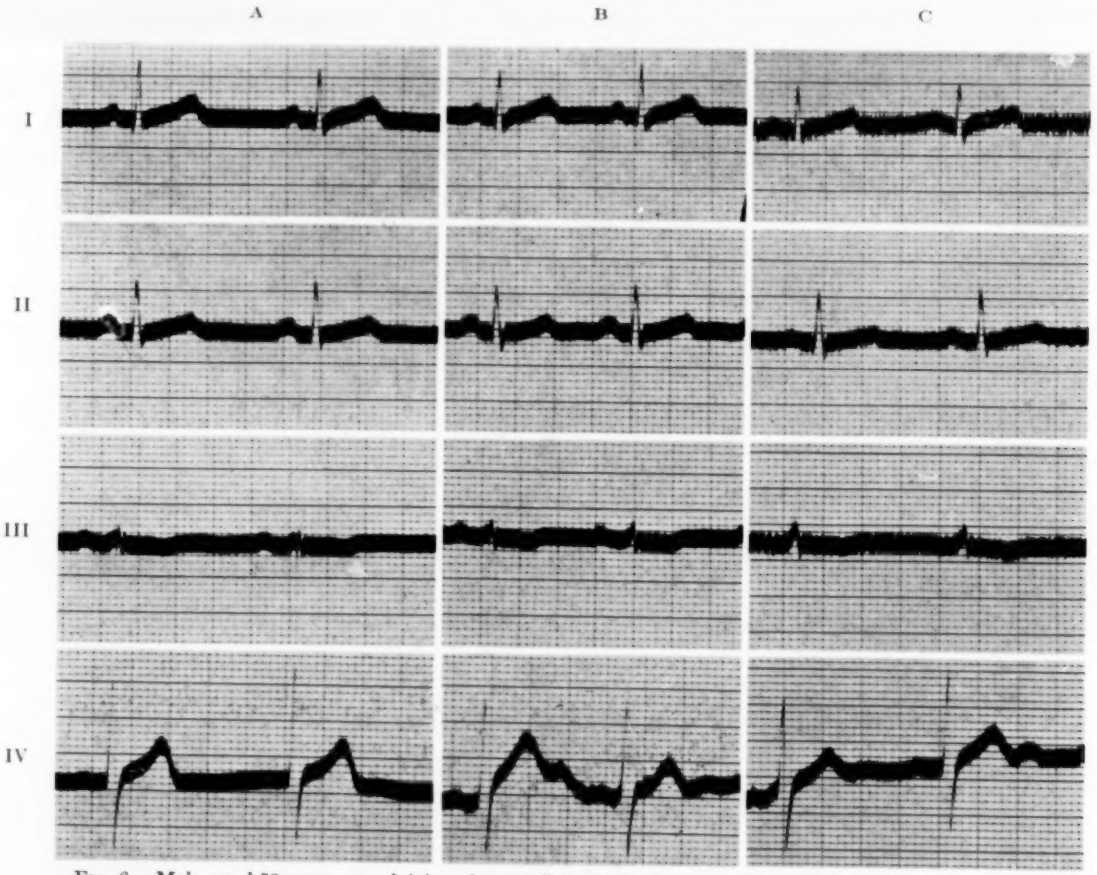


FIG. 6.—Male, aged 53 years, complaining of precordial pain for 6 years. Physical examination negative. Collecting disability insurance and suspected of malingering. *A*, control; a normal record. *B*, after breathing 10% oxygen for 5 minutes. *C*, after 10 minutes; complained of pain; test stopped. No significant changes. In *B*, Lead IV, subject moved to indicate discomfort.

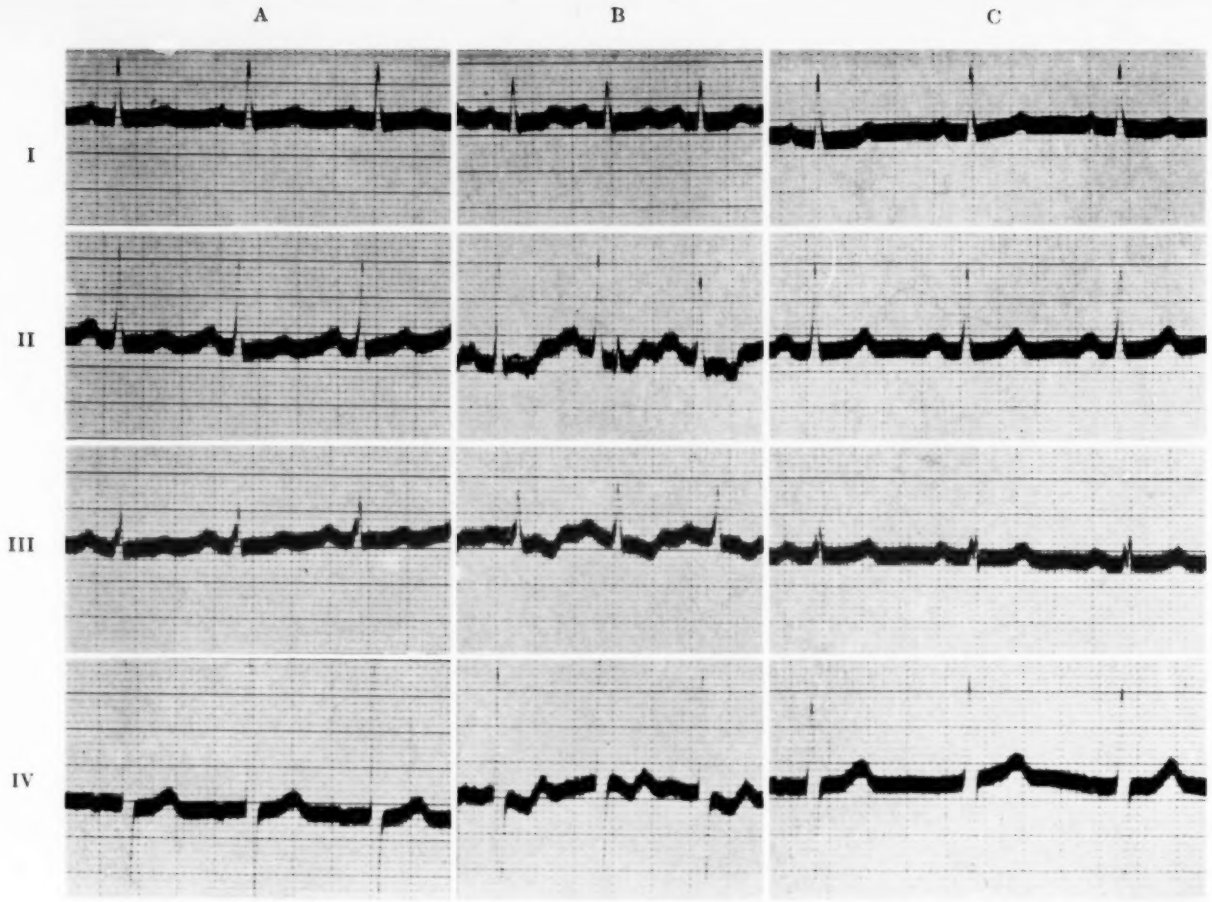


FIG. 7.—Male negro, aged 31 years, with sickle-cell anemia. No evidence of cardiac disease. Hb., 46%; R.B.C., 2,200,000. *A*, control. *B*, after breathing 10% oxygen for 20 minutes; no pain. *C*, after 1 minute of 100% oxygen. There are marked changes in Leads II, III and IV. In *C*, the form of the control is resumed.

of less than 1 mm., is of no significance. It was observed in 22 of 66 supposedly normal persons.

Abnormal. 1. A change in the level of the *RS–T* junction of more than 1 mm. in any lead, even though unassociated with changes in the *T* waves, is abnormal. Its importance is increased if combined with partial or complete reversal in the direction of *T* in Leads I or IVF, or both.

2. Partial or complete reversal in the direction of *T* in Lead I is abnormal when associated with any displacement of the *RS–T* junction in this lead. Such displacement may be as little as 0.5 mm.

3. Complete reversal in the direction of *T* in Lead IVF is always abnormal.

4. Partial reversal of the direction of *T* in Lead IVF, associated with any displacement of the *RS–T* junction in this lead, is abnormal. Such *RS–T* displacement may be as little as 0.5 mm.

Comment. In several of the students in the younger control group, the test was repeated. In 3, changes noted in the first series of records were not observed in the second, or were of lesser degree. In the older control group, the alterations, in general, were not as marked and there was less tendency for variations in repeated tests. The reason for this difference in response is not now apparent (Figs. 2 and 3).

None of the normal persons and none of those with anemia experienced pain during anoxemia. Of 17 with coronary sclerosis and spontaneous attacks of pain, all showed abnormal electrocardiographic responses to the tests (Fig. 4). Twelve complained of pain after varying periods. They were immediately given 100% oxygen, with prompt relief. One patient had suffered an attack of coronary thrombosis 6 months previously. He was having anginal paroxysms on effort and complained of pain during the first test; but 3 months later, when much improved and free from spontaneous pain, he was able to breathe 10% oxygen for the full 20 minutes without discomfort. The difference in the degree of change in the electrocardiograms in tests made at these times portrays graphically the improvement in the coronary circulation (Fig. 5).

In 11 patients with suspected but doubtful coronary disease, the test was negative and confirmed the clinical impression that discomfort was not of cardiac origin. One man, who gave a good description of anginal pain, and who had been collecting disability insurance for 6 years, was suspected of malingering (Fig. 6). Because of the support lent by the test to the examining physician's opinion, it was recommended that disability payments be discontinued.

In 6 patients with previous coronary occlusion and healed myocardial infarcts, the test yielded negative results. One complained of pain and one of mild substernal pressure during the period of anoxemia. The absence of changes in the form of the electrocardio-

FIG. 4.—Male negro, aged 51 years, with sickle-cell anemia. No evidence of cardiac disease. Hb., 40%; R.B.C., 2,200,000. *A*, control. *B*, after breathing 10% oxygen for 20 minutes; no pain. *C*, after 1 minute of 100% oxygen. There are marked changes in Leads II, III and IV. In *C*, the form of the control is resumed.

grams, in view of the fact that these patients were clinically well, may be regarded as indicating that the remaining coronary arteries were able to maintain an adequate flow of blood through the heart muscle. The "coronary reserve" was apparently sufficient to meet the added demands imposed by oxygen want.*

In 5 patients with marked anemia but without signs of cardiac disease, significant changes in the *T* waves occurred in every instance, comparable to those seen in the presence of coronary sclerosis (Fig. 7). Anoxemia added to severe anemia brought about the same result, in this respect, as when added to ischemia; but pain was conspicuously absent. It is also noteworthy that in no case were the *RS–T* junctions displaced more than 1 mm.

Summary. 1. A method has been described for inducing generalized anoxemia without rebreathing, employing an apparatus which enables the subject to breathe a mixture of 10% oxygen and 90% nitrogen at the normal rate of pulmonary ventilation.

2. Changes in the form of the electrocardiogram have been analyzed following the induction of anoxemia in 105 persons, comprising 66 normals, 23 with disease of the coronary arteries, 11 in whom coronary disease was suspected but doubtful, and 5 with severe anemia.

3. Criteria for normal and abnormal responses have been evolved. It is recognized that the material is relatively small and that the criteria must be regarded as tentative. It has not been possible, thus far, to correlate the clinical diagnoses with the anatomic lesions.

4. Changes regarded as abnormal have occurred in patients with clinical symptoms and signs of coronary insufficiency. Similar alterations have been observed in those with anemia but without signs of cardiac disease.

5. There have been no serious untoward effects. Because of two unpleasant reactions, it is suggested that the test should not be given to patients with cardiac insufficiency and should not be repeated in the same patient within 24 hours.

6. Changes in the form of the electrocardiogram caused by induced anoxemia may be used as a clinical test for insufficiency of the coronary circulation, whether this be manifest or latent. An index is afforded of the adequacy of the "coronary reserve." It should be of value in distinguishing pain of coronary origin from pain in the chest due to other causes, as well as from pain referred from the

* In this connection, the comments of Dr. Charles C. Wolferth, of Philadelphia, are of interest. He discussed our paper when it was first presented,[9] and in a recent letter wrote as follows: "One of the striking features of infarction of the lateral or postero-lateral part of the left ventricle is the fact that the electrocardiographic changes appear to be quite transient and after the *RS–T* interval deviations have disappeared there may remain no evidence of myocardial damage, even though later necropsy may reveal the presence of a large infarct. It was this observation that made me raise the point I did in the discussion of your paper. I am inclined to think, therefore, that the presence or absence of change may not depend entirely on the state of the collateral circulation in lesions involving this part of the heart."[14]

abdomen. It is possible that it can be employed also to study, in man, the effect of drugs and of various surgical procedures on the efficiency of the coronary blood flow. Such studies are in progress.

REFERENCES.

(1.) Am. Heart Assn. and Cardiac Soc. of Great Britain and Ireland Joint Recommendations: Am. Heart J., **15**, 107, 1938. (2.) **Dietrich, S.**, and **Schwiegk, H.**: Ztschr. f. klin. Med., **125**, 195, 1933. (3.) **Feil, H.**, and **Siegel,** M. L.: Am. J. Med. Sci., **175**, 255, 1928. (4.) **Greene, C. W.**, and **Gilbert, N. C.**: Arch. Int. Med., **27**, 517, 1921. (5.) **Katz, L. N., Hamburger, W. W.**, and **Schutz, W. J.**: Am. Heart J., **9**, 771, 1934. (6.) **Kountz, W. B.**, and **Hammouda, M.**: Ibid., **8**, 259, 1932. (7.) **Larsen, K.**: Acta med. Scandin., **78**, 141, 1936; Hospitalstidende, **79**, 277, 1936. (8.) **Levy, R. L., Barach, A. L.**, and **Bruenn, H. G.**: Am. Heart J., **15**, 187, 1938. (9.) **Levy, R. L., Bruenn, H. G.**, and **Russell, N. G., Jr.**: Trans. Am. Clin. and Clim. Assn., **53**, 1938 (in press). (10.) **Missall, M. E.**: Ann. Int. Med., **11**, 2018, 1938. (11.) **Parkinson, J.**, and **Bedford, D. E.**: Lancet, **1**, 15, 1931. (12.) **Rothschild, M. A.**, and **Kissin, M.**: Am. Heart J., **8**, 745, 1933. (13.) **Scherf, D.**, and **Goldhammer, St.**: Ztschr. f. klin. Med., **124**, 111, 1933. (14.) **Wood, F. C., Wolferth, C. C.**, and **Bellet, S.**: Am. Heart J., **16**, 387, 1938. (15.) **Wood, F. C., Wolferth, C. C.**, and **Livezey, M. M.**: Arch. Int. Med., **47**, 339, 1931.

SEROLOGIC AND IMMUNOLOGIC STUDIES RELATIVE TO THE VIRUSES OF HUMAN AND SWINE INFLUENZA.*

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During the studies of epidemic influenza previously reported[3] it became important to determine whether the virus strains used in the tissue culture vaccine during the winter of 1936–37 were related immunologically to the virus strain subsequently recovered by ferret and mouse passage from cases of epidemic influenza during the same winter and in the same State Colonies. The present report records such immunologic studies.

Also following the epidemic influenza of 1936–37, Shope,[2] while examining sera from swine suffering from hog cholera in another State Colony, noted the presence in the sera of neutralizing properties against the human influenza virus (PR–8) and the absence in the same sera of such antibodies against the swine influenza virus. (Epidemic influenza had apparently occurred at this Colony, although no nasopharyngeal washings of the inmates were studied.

* Assisted by a grant from the Bureau of Animal Industry, U. S. Department of Agriculture, The Lyophile Serum Fund of the Abington Memorial Hospital, and the International Health Division of the Rockefeller Foundation.

It was particularly significant that the sera of young pigs taken subsequent to the epidemic of influenza showed no neutralizing properties against either virus. Human influenza viruses Phila 37–9 and Phila 37–7 had been obtained from Colonies J. and M. L., respectively,[3] in 1937, the former having been furnished Shope for studies on the sera of swine from this same colony, J.)

In addition to these observations recorded,[2] it appeared desirable to extend the serologic studies over a larger group of viruses, including Phila 37–7, recovered from Colony N. L. There are included, therefore, in the present report studies of the neutralizing properties of the swine sera obtained from the swine in the Colonies against the swine influenza virus (S–15) and against several of the important human influenza virus strains mentioned, including the W.S. (English) strain.

Results of Studies With Human Influenza Virus Used in Tissue Culture Vaccine. *Cross-immunity Tests.* The experience with the strains of human influenza virus Phila 37–7, Phila 37–9 and Phila 37–1 isolated during 1937 in Colonies J. and N. L., and in Philadelphia respectively by ferret and mouse passage from nasopharyngeal washings of ill patients was in agreement with that recorded by Andrewes, Smith and Harris,[4] in the study of a larger number of strains isolated during the same year in England. Not only was it possible to produce cross-immunity in ferrets and mice with these strains isolated in 1937, but a cross-immunity could be produced with all of these strains against the PR–8 virus, the original strain used in the tissue culture vaccine.[3] Since slight antigenic differences, not greatly affecting cross-immunity in animals, have been shown to exist,[1,4] a number of strains* of human influenza virus were used for all vaccine injections in the colonies during the winter of 1937–38.

Cross-neutralization Tests. In Tables 1 and 2 are recorded samples of cross-neutralization tests with sera of ferrets recovered from infection with human influenza virus strains Phila 37–9 and Phila 37–7. These tests showed no cross-neutralizing properties against the swine virus whereas the opposite was true in the tests against the human viruses. There appeared to be slight differences in the rapidity of development of the neutralizing properties against the human viruses. The W.S. (English) strain was not used in all tests due to insufficient serum. Andrewes, Smith and Harris[4] in titrating convalescent ferret sera against different strains of human influenza virus have clearly demonstrated antigenic differences which appear to separate roughly the human viruses used in their studies into three groups. Despite very marked differences found by them cross-neutralization to a greater or lesser extent did occur among all their strains. The marked differences were apparent in but 1 or 2 strains.

* The strains included PR–8, W.S., Melbourne, Phila 37–1, Phila 37–7, Phila 37–9, Phila (1935).

TABLE 1.—CROSS-NEUTRALIZATION TESTS WITH THE SERUM FROM A FERRET BEFORE INFECTION AND FOLLOWING RECOVERY FROM INFECTION WITH THE NEW LISBON STRAIN OF VIRUS.

Ferret E—4 injected intranasally on Jan. 21, 1938 with 0.5 cc. of 2% suspension of mouse lung, infected with virus Phila 37–7 (New Lisbon Strain).

Dates on which blood samples were taken:	Jan. 19.	Jan. 28.	Feb. 1.	Feb. 5.
Virus strain.				
PR–8	4 4 4*	0 0 0	0 0 0	0 0 0
Phila 37–9	4 4 4	0 0 0	0 0 0	0 0 0
Phila 37–7	4 4 4	0 0 0	0 0 0	0 0 0
S–15	N.S.Q.†	4 4 4	4 4 4	N.S.Q.†
W.S.	..	..	..	4 1 1

* The figures represent the degree of lung involvement of the mice as usually expressed in neutralization tests, *i. e.*, 4 represents complete consolidation of the lungs, while 2 represents consolidation of approximately one-half of the lungs.

† Not a sufficient quantity of serum obtained for testing.

TABLE 2.—CROSS-NEUTRALIZATION TESTS WITH THE SERUM FROM A FERRET BEFORE INFECTION AND FOLLOWING RECOVERY FROM INFECTION WITH THE JAMESBURG STRAIN OF VIRUS.

Ferret E—5 injected intranasally on Jan. 21, 1938 with 0.5 cc. of 2% suspension of mouse lung, infected with virus Phila 37–9 (Jamesburg Strain).

	Mouse Lung Involvement.			
Dates on which blood samples were taken:	Jan. 19.	Jan. 28.	Feb. 1.	Feb. 5.
Virus strain.				
PR–8	4 4 4*	2 2 2	0 0 0	0 0 0
Phila 37–9	4 4 4	1 1 1	1 0 0	0 0 0
Phila 37–7	4 4 4	1 1 1	0 0 0	0 0 0
S–15	4 4 4	4 4 4	4 4 4	4 4 4
W.S.	..	..	..	0 0 0

* The figures represent the degree of lung involvement of the mice as usually expressed in neutralization tests, *i. e.*, 4 represents complete consolidation of the lungs, while 2 represents consolidation of approximately one-half of the lungs.

From these results it is evident that the viruses used in the chick embryo tissue culture vaccine had a close antigenic relationship to the viruses recovered in the State Colonies, one-third of whose inmates had received the vaccine. This would appear to strengthen the evidence obtained suggesting the value of such vaccine as an immunizing agent against epidemic influenza.[3]

Results of Cross-neutralization Tests on Swine Sera. *Sera.* The samples of swine sera were kindly sent us by Dr. R. E. Shope, who had obtained them from swine on the Bordentown State Prison Farm and on the farm of the Jamesburg Reform School. The swine sera marked "young pigs" were from animals born and bled after the 1937 influenza epidemic and the swine sera marked "old pigs" were from animals born before the 1937 influenza epidemic and bled after the epidemic. The herds of swine and their contacts with the inmates of the colonies has been previously mentioned.[2]

Viruses. The virus strains employed in the neutralization tests were the human influenza virus strains PR–8 (Francis); English W.S. (Wilson Smith); Phila 37–9 (Jamesburg); Phila 37–7 (New Lisbon); and the swine influenza virus strain S 15 (Shope).

All virus suspensions used in the tests were 2% suspensions of infected mouse lung with the above respective strains except for Phila 37–7 which was a 5% suspension. The sera and virus suspension were added in equal proportions and incubated at 37° C. Six anesthetized Swiss mice were inoculated intranasally by means of a pipette with 0.05 cc. of the mixture.

TABLE 3.—NEUTRALIZATION TESTS ON SWINE SERA COLLECTED FROM BORDENTOWN PRISON FARM, NEW JERSEY.

Serum from swine, No.	Serum Tested Against: Swine influenza virus Strain 15. Pulmonary lesion mouse. 1	2	3	4	5	6	Protection.	Human influenza virus strain PR-8. Pulmonary lesion mouse. 1	2	3	4	5	6	Human influenza virus strain Phila 37-9 (Jamesburg). Pulmonary lesion mouse. 1	2	3	4	5	6	Human influenza virus strain Phila 37-7 (New Lisbon). Pulmonary lesion mouse. 1	2	3	4	5	6	Protection.	English. W.S. Pulmonary lesion mouse. 1	2	3	4	5	6	Protection.
Young pigs	Born after July, 1937.																															
T1	D7*	D7	D7	D8	D9	D9	NP†	D6	D6	D6	D7	D8	D8	NP	D6	D6	D7	D7	D7	D8	NP	D8	3+‡	3+	2+	0	0	PP							
T2	D5	D5	D6	D7	D8		NP	D5	D6	D6	D7	D7	D7	NP	D4	D4	D4	D6	D6	D7	NP	D5	D7	D7	D8	D8	D8	NP	D4	D6	D6	D6	D7	D7	NP
T3	D5	D8	D8	D9			NP	D7	D7	D8	D8	D8		NP	D4	D4	D4	D8	D8	D8	NP	D6	D6	D6	D7	D8	D10	NP							
T4	D2	D4	D4	D7	D8	D10	NP	D5	D5	D6	D7	D9	D9	NP	D4	D4	D4	D5	D5	D5	NP	D8	D8	3+	3+	3+	2+	NP	D6	D6	D6	D6	D6	2+	NP
T5	D6	D7	D8	D10	D10	D10	NP	D4	D4	D5	D6	D6	D6	NP	D4	D4	D8	D8	D10	D10	NP	D6	D7	D7	D8	D8	D8	NP							
T6	D8	D10	3+	3+	3+	3+	NP	D3	D5	D5	D6	D6	D6	NP	D4	D5	D5	D5	D6	D6	NP	D9	3+	3+	3+	3+	3+	NP	D4	D4	D4	D4	D6	D6	NP
T7	D6	D7	D7	D8	D8	D9	NP		D5	D8	D8	D10	2+	NP	D8	D9	D10	D10	D10	3+	NP	D10	D10	3+	3+	3+	3+	NP							
T8	D6	D6	D7	D8	D9	3+	NP	D4	D4	D5	D5	D6	D6	NP	D4	D4	D4	D4	D5	D5	NP	D5	D6	D6	D6	D6	D7	NP	D3	D4	D4	D4	D4	D4	NP
Normal sera	D5	D5	D5	D5	D7	D7	..	D4	D4	D5	D5	D5	D5	..	D5	D5	D5	D6	D6	D8	..	D6	D6	D7	D7	D7	D9	..	D4	D4	D4	D4	D4	D6	
Sick pigs	Pigs born before Nov., 1936.																															
2	D6	D7	D7	D7	D7	D7	NP	D3	1+	1+	1+	1+	0	IP	1+	0	0	0	0	0	CP	0	0	0	0	0	0	CP							
3	D6	D6	D7	D8	D8	D8	NP	D3	1+	1+	1+	0	0	IP	1+	1+	1+	1+	1+	0	CP	0	0	0	0	0	0	CP							
Old pigs																																			
4	D8	D10	3+	3+	2+	2+	PP	1+	0	0	0	0	0	CP	2+	0	0	0	0	0	CP	0	0	0	0	0	0	CP							
5	D5	D5	D5	D7	D7	D7	NP	D6	1+	0	0	0	0	IP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP							
7	D5	D5	D8	3+	3+	2+	PP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP							
8	D6	D6	D7	D8	D8	D9	NP	2+	2+	1+	0	0	0	IP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP	1+	1+	0	0	0	0	CP
9	D5	D5	D6	D6	D7	3+	NP	3+	2+	2+	1+	1+	0	PP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP							
10	D4	D4	D5	D5	D5	D7	NP	1+	0	0	0	0	0	CP	0	0	0	0	0	1+	CP	1+	0	0	0	0	0	CP							
11	D7	D8	D10	D10	3+	3+	NP	2+	0	0	0	0	0	CP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP							
12	D5	D8	D9	D9	D9	D9	NP	D9	2+	2+	2+	2+	2+	PP	1+	1+	0	0	0	0	CP	0	0	0	0	0	0	CP	2+	2+	1+	0	0	0	IP
13	D7	D7	D7	D8	D9	D10	NP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP							
14	D7	D7	D8	D8	D9	D9	NP	1+	1+	1+	0	0	0	CP	1+	0	0	0	0	0	CP	1+	0	0	0	0	0	CP	2+	0	0	0	0	0	CP
15								D7	D8	D9	2+	2+	1+	CP	1+	1+	1+	0	0	0	CP	3+	3+	2+	2+	1+	1+	PP							
16	D10	D10	3+	2+	2+	2+	PP	1+	1+	0	0	0	0	CP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP							
17	3+	2+	0	0	0	0	PP	D6	D7	0	0	0	0	PP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP							
18	D10	D10	3+	3+	3+	3+	PP	2+	0	0	0	0	0	CP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP							
19	D9	D10	D10	D10	D10	3+	NP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP	1+	0	0	0	0	0	CP
20	D6	D6	D7	D7	D8	D9	NP	D3	D4	D5	3+	3+	3+	NP	D6	3+	3+	2+	2+	1+	PP	D7	2+	2+	2+	2+	2+	PP	D8	D9	D10	D10	3+	3+	NP
21	D3	D5	D5	D6	D6	D7	NP	D4	D10	D10	D10	D10	D10	NP	D9	D10	D10	3+	3+	3+	NP	D9	D9	D10	2+	2+	2+	NP							
Normal sera	D4	D4	D5	D6	D7	D9	..	D4	D4	D5	D6	D6	D6	..	D4	D5	D5	D6	D6	D6	..	D6	D6	D6	D7	D7	D7	..	D4	D4	D6	D6	D6	D8	

* D7—Mouse died on seventh day.
† NP—No protection.
‡ 3—Mouse killed on tenth day and lung showed about three-fourths involvement.

PP—Partial protection.
IP—Incomplete protection.
CP—Complete protection.

TABLE 4.—NEUTRALIZATION TESTS ON SWINE SERA COLLECTED FROM JAMESBURG STATE HOME FOR BOYS.

Serum from swine, No.	Serum Tested Against: Swine influenza virus Strain 15. Pulmonary lesion mouse. 1	2	3	4	5	6	Protection.	Human influenza virus strain PR–8. Pulmonary lesion mouse. 1	2	3	4	5	6	Protection.	Human influenza virus strain Phila 37–9 (Jamesburg). Pulmonary lesion mouse. 1	2	3	4	5	6	Protection.	Human influenza virus strain Phila 37–7 (New Lisbon). Pulmonary lesion mouse. 1	2	3	4	5	6	Protection.	English. W.S. Pulmonary lesion mouse. 1	2	3	4	5	6	Protection.
Young pigs	Born after July, 1937.																																			
1	D6	D6	D6	D6	D6	D6	NP	D5	D6	D6	D7	D7	D7	NP	D4	D4	D4	D4	D4	D4	NP	D7	D8	D8	D8	3+	3+	NP								
2	D6	D6	D7	D7	D7	D7	NP	D7	D7	D8	D8	D9	D9	NP	D6	D7	D7	D8	D8	D9	NP	D8	D8	D8	D9	3+	2+	NP								
3	D6	D6	D8	D8	D8	D10	NP	D4	D5	D5	D6	D6	D7	NP	D4	D4	D5	D5	D5	D6	NP	D6	D7	D7	D8	D8	0	NP								
5	D5	D5	D5	D6	D7	D8	NP	D7	D8	D8	D8	D9	D9	NP	D7	D7	D8	D8	D9	3+	NP	D9	3+	3+	3+	2+	2+	NP								
6	D5	D7	D7	D7	D7	D9	NP	D6	D6	D6	D6	D7	D9	NP	D4	D6	D6	D6	D6	D6	NP	D9	D9	D9	4+	3+	3+	NP	D3	D3	D4	D4	D4	D4	NP
7	D5	D5	D5	D6	D6	D8	NP	D4	D5	D6	D6	D7	D8	NP	D4	D5	D5	D5	D5	D5	NP	D5	D5	D6	D6	3+	0	NP								
Normal sera	D5	D5	D5	D6	D7	D9	..	D6	D6	D6	D6	D7	D7	..	D4	D4	D5	D5	D5	D7	..	D6	D6	D7	D7	D8	D8	..	D4	D4	D4	D4	D4	D4	
Old pigs	Born before Nov., 1936																																			
1	D5	D5	D5	D7	D8	D9	NP	3+	3+	3+	3+	2+	2+	PP	3+	2+	1+	1+	1+	1+	PP	1+	0	0	0	0	0	CP								
2	D4	D5	D5	D6	D6	D6	NP	3+	2+	2+	1+	1+	1+	PP	3+	3+	3+	3+	3+	3+	PP	2+	1+	1+	0	0	0	IP								
3	D8	D8	D9	D9			NP	2+	2+	1+	1+	1+	0	IP	3+	2+	2+	1+	1+	0	PP	0	0	0	0	0	0	CP								
4	D5	D5	D5	D6	D6	D7	NP	D6	D6	D7	D8	D8	D8	NP	D5	D5	D5	D7	D7	D7	NP	D5	2+	2+	1+	1+	1+	PP								
5	D7	D9	D9	D9	D9	D9	NP	2+	2+	1+	1+	1+	0	IP	3+	3+	2+	2+	2+	1+	PP	0	0	0	0	0	0	CP								
6	D5	D7	D7	3+	2+	1+	NP	D6	D6	D6	D6	D7	D8	NP	D5	D5	D5	D5	D5	D5	NP	D9	4+	3+	3+	2+	2+	NP								
7	D7	D7	D8	D9	D9	D9	NP								D5	D7	D7	D7	D8	D8	NP	1+	0	0	0	0		CP								
8	D5	D6	D6	D8	D8	D8	NP	2+	1+	1+	0	0	0	IP	2+	2+	2+	0	0	0	IP	0	0	0	0	0	0	CP	3+	3+	2+	2+	2+	1+	PP
9	D6	D6	D8	D9	D9	3+	NP	D7	D7	D7	D7	D7	D9	NP	D5	D5	D5	D5	D6	3+	NP	3+	3+	2+	2+	2+	2+	NP								
10	D5	D5	D5	D5	D7	D8	NP	1+	1+	1+	1+	0	0	CP	3+	3+	2+	2+	2+	2+	PP	0	0	0	0	0	0	CP								
11	D6	D6	D7	D8	D9	D9	NP	3+	3+	3+	2+	2+	1+	PP	3+	3+	2+	2+	1+	1+	PP	0	0	0	0	0	0	CP	3+	3+	3+	3+	3+	1+	PP
12	D7	D7	D7	D8	D8	D9	NP	D5	D6	D6	D7	D8	D9	NP	D7	D7	D7	D7	3+	2+	NP	0	0	0	0	0	0	CP								
13	D6	D7	D8	D9	D9	D9	NP	D9	D9	D9	D10	3+	3+	NP	D10	D10	D10	D10	3+	3+	NP	2+	2+	1+	1+	1+	0	IP								
14	D8	D8	D8	D9	D9	D10	NP	D1	D2	D8	D9	D10	3+	NP	D4	3+	3+	2+	2+	2+	PP	D5	0	0	0	0	0	CP								
15	D5	D6	D7	D7	D8	D8	NP	D4	D6	D6	D8	D10	D10	NP	D4	D4	D4	D5	D6	D7	NP	3+	3+	3+	2+	2+	2+	PP	D6	D6	D6	D7	D7	D9	NP
16	D3	D7	D8	D10	D10	D10	NP	3+	3+	3+	2+	2+	2+	PP	3+	3+	3+	2+	2+	2+	PP	0	0	0	0	0	0	PP	0	0						
17	D10	D10	D10	D10	3+	3+	NP	D3	0	0	0	0	0	IP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP
18	D7	D7	D8	D8	D9	D9	NP	2+	2+	1+	1+	0	0	IP	1+	1+	0	0	0	0	CP	0	0	0	0	0	0	CP								
19	D6	D7	D7	D8	D9	D10	NP	3+	3+	2+	2+	2+	0	PP	D4	2+	2+	1+	1+	1+	IP	0	0	0	0	0	0	CP								
20	D8	D8	D9	D9	D9	D9	NP	1+	1+	1+	1+	1+	0	CP	D5	2+	1+	1+	1+	1+	IP	0	0	0	0	0	0	CP	0	0	0	0	0	0	CP
Normal sera	D4	D4	D6	D6	D6	D9	..	D5	D5	D5	D5	D5	D6	..	D4	D4	D5	D5	D6	D6	..	D5	D5	D6	D8	D8	D8	..	D4	D4	D4	D4	D4	D4	

‡ 5—Mouse killed on tenth day and lung showed about three-fourths involvement.

The experiment terminated at the end of the tenth day and all surviving mice were killed and the lungs were examined for gross pulmonary lesions.

Tables 3 and 4 record the cross-neutralization tests against the strains of influenza virus mentioned. They are not strictly comparable to the tests recorded by Shope, since in these present studies 6 mice were used for each cross-neutralization test and the surviving mice were not killed until the tenth day. In general, however, the tests are quite comparable and although a larger number of virus strains were used in the present studies, nevertheless among the tests of those strains used in both studies there was satisfactory agreement. At Colony B all sera obtained from pigs born after July, 1937, showed no neutralizing properties against any strain of human or swine influenza virus, whereas most of the sera obtained from pigs born before November, 1936, showed marked neutralizing properties against all of the human virus strains used, although none against the swine strain. A few exceptions may be noted such as Nos. 15, 20 and 21 which suggest the existence of slight antigenic differences between the human virus strains. There was an insufficient amount of serum in the case of No. 15 to make a test against the swine virus.

The antigenic differences among the human strains appeared more significant in the cross-neutralization tests on the sera from the herd of swine attached to Colony J, from which virus strain Phila 37–9 was obtained. For example, in Pigs 4, 9, 12, 13 and 14 the differences are very striking in the neutralization tests against the two viruses, Phila 37–9 and Phila 37–7. Since virus Phila 37–7 had never been as virulent in mice as Phila 37–9 a 5% suspension of Phila 37–7 had been used as mentioned rather than the 2% suspension used for Phila 37–9. This permitted a direct comparison of the neutralizing properties of the sera since all of the controls for each virus died in a comparable period (Tables 3 and 4). In Colony J, also, the sera of young pigs born after July, 1937, showed no neutralizing properties against either the swine or human virus, whereas those born before November, 1936, in most instances, showed partial or complete neutralization of the human virus strains.

It will be noted in a comparison of the results shown in Table 4 with those recorded by Shope[2] that serum from old Pig 7 showed no neutralizing properties against strain Phila 37–9 in the present studies, whereas repeated tests of this serum by Shope confirmed an antigenic difference between strains Phila 37–9 and PR–8. Insufficient serum from this pig was available to check further these findings in the present studies. In other respects, the two studies were in essential agreement.

Discussion. The close relationship of all strains of human influenza virus so far isolated is emphasized by the results of the present studies on cross-immunity and cross-neutralization with viruses isolated from different localities during the mild pandemic of influenza of 1936–37. A comparison with strains from previous years and from other parts of the world gives added confirmation to this

relationship. The antigenic differences in certain strains, however, should not be disregarded nor should there be overlooked the apparent lack of marked significance of these differences as far as they are related to cross-immunity. From these results it would seem worthwhile to use at least several strains of virus chosen for their antigenic differences in the development of a chick embryo tissue culture vaccine.

The cross-neutralization studies on swine sera initiated by Shope and carried on with a larger number of virus strains at the Children's Hospital also afforded the opportunity of studying antigenic differences in strains of virus isolated in this Laboratory and originally transmitted to the swine under ordinary or natural field conditions: a fact which should make the cross-neutralization tests on the sera of even greater significance.

Summary. 1. The immunologic and serologic relationships between the human influenza viruses used as a vaccine and the human influenza viruses isolated in the Colonies vaccinated during a subsequent epidemic of influenza are described.

2. The development of neutralizing antibodies against the human virus in the sera of swine exposed to human epidemic influenza and the absence in the same sera of corresponding antibodies for the swine virus are described. The appearance in the cross-neutralization tests of antigenic differences in the human influenza viruses isolated is also described and discussed.

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REFERENCES.

(1.) **Magill, T. P.**, and **Francis, T., Jr.**: Proc. Soc. Exp. Biol. and Med., **35**, 463, 1936. (2.) **Shope, R. E.**: J. Exp. Med., **67**, 739, 1938. (3.) **Stokes, J., Jr., McGuinness, A. C., Langer, P. H., Jr.**, and **Shaw, D. R.**: Am. J. Med. Sci., **194**, 757, 1937. (4.) **Stuart-Harris, C. H., Andrewes, C. H.**, and **Smith, W.**: Med. Res. Coun., Spec. Ser. 228, Sect. VI, p. 125, 1938.

COMPLEMENT-FIXATION STUDIES ON THE SERA OF INDIVIDUALS VACCINATED WITH ACTIVE VIRUS OF HUMAN INFLUENZA.*

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The present report concerns studies of the complement-fixing antibodies in the sera of individuals vaccinated with the active

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virus of human influenza during 1937 and 1938 and in the sera of a group of controls in large State Colonies, as previously described.[5] There are included studies of the sera of individuals suffering from respiratory infections, non-influenzal in type, during the late winter and spring of 1938.

Wilson Smith[4] first demonstrated a complement-fixation test for the titration of influenzal antibodies in the sera of men and experimental animals, also showing a fairly close correlation between this test and the neutralization test on the same sera. Fairbrother and Hoyle[1,3a] also described a complement-fixation test for antibodies in human sera and later[3b] demonstrated that "the complement fixing antigen is a soluble substance probably liberated during multiplication of the virus in the tissues." This observation is of significance in relation to the production of complement-fixing antibodies as a result of vaccination. According to such findings the complement-fixing antibody response should depend upon the type of vaccine used, whether infected mouse lung or tissue culture vaccine.

Francis *et al.*[2] made the first extensive study of complement-fixation and neutralization tests on the same sera obtained from individuals during both the acute and convalescent stages of epidemic influenza. Parallel tests were also made by the same workers upon the sera of individuals in close contact with influenzal patients, and upon the sera of others with non-influenzal respiratory infections. In these studies the titers of both antibodies were markedly increased by acute influenzal attacks, whereas there were but slight increases in the sera of the contact cases, and no increase in the sera of those suffering from non-influenzal infections.

Since in the present studies large numbers of individuals had been vaccinated with active human influenza virus as previously reported,[5] it was important to determine the effect of such vaccine injections upon the complement-fixing antibodies of their sera, together with a similar and simultaneous study of the sera of a group of non-vaccinated controls. It was possible also to fulfill partially a general objective of studying the sera of the same individuals over a period of 1 to 2 years under similar well-controlled environmental conditions but in the presence of a variety of intercurrent respiratory infections.

Technique of Complement-fixation Test. *Antigen.* Healthy white Swiss mice were inoculated intranasally under ether, with a 10% suspension of mouse lung infected with the PR–8 virus strain. These mice were killed when moribund, and the lungs removed aseptically and ground in a mortar with sterile powdered glass. Normal saline, 1.5 cc., was added per lung and the suspension centrifuged at 3000 r.p.m. for 30 minutes. The supernatant was filtered through a Type V Berkefeld filter and bottled in 20 cc. amounts in sterile bottles. The antigen was stored at $-10°$ to $-15°$ C. and the titer was found to remain fairly constant after the first week of storage and did not become anticomplementary upon standing 8 weeks at this temperature.

The antigen was titrated each time before using for hemolytic, anticomplementary and antigenic units and was then diluted so that 0.5 cc. contained 5 antigenic units.

Antigen was also prepared from virus grown on minced chick embryo in Tyrode's solution. The antigenic titer of this preparation was very low and unsatisfactory for use. Antigen prepared from tissue culture which had been preserved by drying *in vacuo* at a low temperature and regenerated to one-half its original volume gave a high antigenic titer in some instances.

Due to the factor that the vaccine, which was injected into individuals at the various State Colonies was prepared from tissue cultures of the virus strain, the better antigen for use in testing sera from vaccinated individuals was that prepared from infected mouse lungs.

Known positive sera tested against normal mouse lung antigen and tissue culture antigen with no virus gave negative results.

Complement. Fresh guinea pig sera were titrated and diluted so that 3 minimal hemolytic doses were contained in 1 cc. of diluted serum.

Sera. A pool of immune rabbit sera was used as the standard each time. The rabbits were immunized against PR–8 virus strain grown on minced chick embryo culture medium. The titer of the standard pool was 1 to 256 for complement-fixing antibodies and 1 to 320 for neutralizing antibodies.

All sera had been collected and stored under sterile conditions. The sera were kept at 3° C. until tested and then were inactivated by heating at 56° C. for 30 minutes.

The test was set up according to Table 1.

TABLE 1.—COMPLEMENT–FIXATION TEST FOR INFLUENZA.

Tube:	1	2	3	4	5	6	7	8
Serum diluted:	Undil.	1 : 4	1 : 8	1 : 16	1 : 32	1 : 64	1 : 128	Contro
	0.5 cc.	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Antigen-infected mouse lung with PR–8 virus (Berkefeld filtered 5 units in 0.5 cc.) .	0.5 cc.	0.5	0.5	0.5	0.5	0.5	0.5	
Room Temperature for 15 Minutes.								
Complement, 3 units in 1 cc.	1 cc.	1	1	1	1	1	1	1
Incubate 2 hours, 37° C.—water-bath.	Overnight 3° to 6° C.—icebox.							
Antisheep amboceptor, 2 units in 0.5 cc. . . .	0.5 cc.	0.5	0.5	0.5	0.5	0.5	0.5	0.5
2% sheep cells	0.5 cc.	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Incubate 1 hour, 37° C.—water-bath.								

The results were read immediately upon taking the tubes from the water-bath and again after a sufficient time in the icebox, to allow the sedimentation of the suspended sheep cells. Final readings were made at this time, and the end point was considered as the last tube in which complete fixation occurred. As a rule, the end points were quite sharp.

Results. A study was made during the recent winter, 1937–38, when epidemic influenza was absent, of sera obtained from individuals both during the acute and convalescent stages of respiratory infections. Nose and throat washings were collected from many of these individuals but no influenza virus was obtained following ferret passage. Table 2 indicates the complement-fixing antibodies in such sera from groups of vaccinated and non-vaccinated individuals, whose febrile response and general type of respiratory infection are also recorded. These groups of individuals at Colony S represented the only epidemic of respiratory infection of any significance occurring in the State Colonies studied during this winter, 1937–38, and the incidence in the vaccinated and non-vaccinated

groups was almost identical. Whether such infections occurred in the vaccinated or non-vaccinated group there appeared to be no difference in the titer of complement-fixing antibodies. Also in comparing the sera from the acute and convalescent stages of both groups the titer was fairly constant.

TABLE 2.—SKILLMAN COLONY—VACCINATED GROUP.

	Complement-fixation test on blood samples collected.		Clinical history.		
	2-8-38	2-28-38			
Name.	Complete fixation in serum dilution.		Date, hosp.	Highest temp. °C.	Diagnosis.
M. H.	1 : 16	1 : 16	2- 7-38	100.0	U. R. I.
R. H.	1 : 16	1 : 16	2- 7-38	100.2	U. R. I.
N. C.	1 : 16	1 : 16	2- 6-38	105.0	U. R. I.
P. B.	1 : 32	1 : 16	2- 8-38	101.2	Otitis media
A. D.	1 : 4	0	2- 8-38	100.4	U. R. I.
C. B.	0	0	2- 6-38	104.6	U. R. I.
C. A.	1 : 16	1 : 4	2- 8-38	101.0	U. R. I.
	2-23-38	3-14-38			
E. J.	1 : 8	1 : 4	2-21-38	98.2	U. R. I.
S. B.	1 : 8	1 : 8	2-21-38	100.6	U. R. I.
W. C.	1 : 4	0	2-20-38	103.0	U. R. I.
	Non-vaccinated Group.				
	2-8-38	2-28-38			
B. W.	1 : 16	1 : 8	2- 7-38	102.0	U. R. I.
E. Y.	1 : 64	1 : 32	2- 7-38	101.4	U. R. I.
N. C.	1 : 8	1 : 8	2- 6-38	100.0	U. R. I.
E. W.	1 : 16	1 : 8	2- 5-38	100.0	U. R. I.
H. S.	1 : 32	1 : 8	2- 7-38	100.8	U. R. I.
C. M.	1 : 32	1 : 32	2- 8-38	102.0	U. R. I.
H. G.	0	0	2- 8-38	101.2	U. R. I.
S. M.	1 : 4	1 : 4	2- 8-38	105.4	Otitis media
R. H.	0	0	2- 8-38	102.2	U. R. I.
	2-23-38	3-14-38			
J. R.	0	0	2-21-38	102.2	U. R. I.
B. M.	1 : 2	0	2-21-38	101.0	U. R. I.
F. M.	1 : 8	1 : 8	2-21-38	99.2	U. R. I.
J. H.	1 : 2	0	2-21-38	100.0	U. R. I.
F. W.	1 : 4	1 : 4	2-21-38	101.0	U. R. I.
R. M.	0	0	2-21-38	100.2	U. R. I.
P. M.	1 : 2	0	2-20-38	100.2	U. R. I.
C. P.	0	0	2-22-38	101.4	U. R. I.
J. L.	1 : 16	1 : 16	2-21-38	101.0	U. R. I.
L. S.	0	0	2-21-38	101.0	U. R. I.
J. L.	1 : 4	1 : 2	2-21-38	99.6	U. R. I.

In a determination of the fluctuation of complement-fixing antibodies in the sera of hospital personnel during the seasonal height of respiratory infections, sera were obtained from physicians, nurses and social workers at the Children's Hospital during the late winter and early spring of 1938, as shown in Table 3. No significant changes for the three determinations are noted, except for a possible tendency to a decrease in titer.

Tables 4 and 5 record the titers in the sera of a vaccinated and a non-vaccinated group of individuals from Colony N.L. over a period of 2 years. The sera in both years were obtained before vaccine injections were given and again 2 weeks following the final vaccine injection. In the winter of 1936–37 the sera were obtained before the occurrence of epidemic influenza.

In Tables 6 and 7 are recorded comparisons of the titers of sera obtained at Colonies S and J from two groups of individuals, vacci-

TABLE 3.—COMPLEMENT-FIXATION TEST ON CONTROL GROUP.
(Age, over 21 years.)

Name.	Blood samples collected. 1-11-38	2-21-38	4-20-38
I. W.	1 : 4	1 : 4	No sample
D. S.	1 : 8	1 : 8	1 : 4
E. N.	1 : 4	1 : 4	1 : 4
P. S.	1 : 4	1 : 4	1 : 2
E. K.	0	0	0
J. M.	1 : 2	0	0
J. A.	1 : 2	0	1 : 2
A. W.	1 : 4	1 : 2	No sample
M. R.	1 : 4	1 : 2	No sample
M. M.	0	0	0
L. G.	1 : 4	1 : 2	1 : 2
A. M.	No sample	0	0

TABLE 4.—NEW LISBON COLONY—VACCINATED GROUP.

Name.	Complement-fixation test on blood samples collected. 10-29-36	12-22-36	Sickness.	10-4-37	2-14-38	Sickness.
	Complete Fixation in Serum Dilutions.					
K. G.	0	1 : 4	U. R. I.	1 : 8	1 : 8	Cold
S. K.	1 : 4	1 : 4	U. R. I.			
J. C.	1 : 32	1 : 64	U. R. I.	1 : 8	1 : 32	Colds
G. R.	1 : 32	1 : 64	Colds			
G. D.	1 : 32	1 : 32	Colds	1 : 16	1 : 32	No U. R. I.
E. B.	1 : 8	1 : 32	U. R. I.			
J. S.	1 : 4	1 : 4	No U. R. I.	1 : 8	1 : 4	Cold
L. S.	1 : 4	1 : 4	U. R. I.	1 : 2	0	No U. R. I.
G. H.	1 : 32	1 : 32	Cold	1 : 8	1 : 4	No U. R. I.
C. B.	1 : 64	1 : 32	Colds			
E. P.	1 : 8	1 : 32	Colds	1 : 8	1 : 8	Colds
G. C.	1 : 4	1 : 8	No U. R. I.	1 : 8	1 : 16	No U. R. I.
F. C.	0	1 : 2	Colds	1 : 16	1 : 16	Colds
S. C.	0	0	Colds	1 : 2	1 : 2	Colds
W. P.	1 : 4	1 : 8	Colds	1 : 8	1 : 8	Colds
W. T.	1 : 4	1 : 8	No U. R. I.	1 : 4	1 : 4	No U. R. I.
C. M.	..	..	...	1 : 4	1 : 4	No U. R. I.
E. S.	..	..	...	1 : 16	1 : 32	Colds
W. C.	..	..	...	1 : 16	1 : 32	Colds
W. K.	..	..	...	0	0	No U. R. I.
C. B.	..	..	...	1 : 32	1 : 16	No U. R. I.
P. M.	..	..	...	1 : 4	1 : 4	Cold
W. M.	..	..	...	1 : 8	1 : 32	Cold
G. W.	..	..	...	1 : 2	1 : 2	No U. R. I.
B. B.	..	..	...	1 : 8	1 : 8	No U. R. I.

TABLE 5.—NEW LISBON COLONY—NON-VACCINATED GROUP.

Name.	Complement-fixation test on blood samples collected. 10-29-36	12-22-36	Sickness.	10-4-37	2-14-38	Sickness.
	Complete Fixation in Serum Dilutions.					
N. S.	1 : 32	1 : 64	Cold	1 : 64	1 : 64	No U. R. I
F. G.	0	0	Cold	1 : 4	1 : 4	No U. R. I.
T. S.	1 : 4	1 : 4	U. R. I.	1 : 8	1 : 16	No U. R. I.
E. H.	0	0	No U. R. I.	0	0	No U. R. I.
E. P.	0	1 : 8	No U. R. I.	1 : 16	1 : 16	No U. R. I.
C. M.	1 : 8	1 : 8	Cold	1 : 4	1 : 4	No U. R. I.
G. W.	0	1 : 4	No U. R. I.	1 : 2	1 : 4	No U. R. I.
C. W.	0	1 : 8	Cold			
D. W.	0	0	No U. R. I.			
J. S.	1 : 16	1 : 8	No U. R. I.			
P. M.	1 : 8	1 : 16	No U. R. I.			
J. N.	0	1 : 16	No U. R. I.			
G. R.	1 : 4	1 : 4	U. R. I.			
P. A.	0	1 : 16	U. R. I.			
H. R.	0	1 : 8	Cold			
M. S.	..	..	...	0	0	Cold
T. J.	..	..	...	1 : 8	1 : 8	U. R. I.
P. P.	..	..	...	0	0	No U. R. I.
C. C.	..	..	...	1 : 8	0	No U. R. I
H. W.	..	..	...	0	0	No U. R. I.
D. W.	..	..	...	1 : 8	1 : 8	No U. R. I.
R. J.	..	..	...	1 : 16	1 : 16	No U. R. I.

TABLE 6.—SKILLMAN COLONY—VACCINATED GROUP.

Name.	Complement-fixation test on blood samples collected. 9-23-37 Complete fixation in serum dilutions.	2-15-38 Complete fixation in serum dilutions.	Clinical history.	
A. B.	1 : 32	1 : 64	No illness	
B. H.	1 : 8	1 : 8	No illness	
B. C.	1 : 16	1 : 16	No illness	
M. B.	1 : 32	1 : 32	No illness	
S. C.	1 : 8	1 : 8	No illness	
M. F.	1 : 16	1 : 16	No illness	
J. A.	1 : 8	1 : 8	No illness	
O. F.	1 : 8	1 : 8	No illness	
W. B.	1 : 8	1 : 8	No illness	
A. B.	1 : 8	1 : 16	No illness	
E. C.	1 : 16	1 : 16	No illness	
I. B.	1 : 8	1 : 8	No illness	
S. B.	1 : 8	1 : 16	No illness	
J. W.	1 : 8	1 : 8	No illness	
H. C.	1 : 8	1 : 2	No illness	
M. D.	0	0	No illness	
A. H.	1 : 16	1 : 4	No illness	
E. A.	1 : 8	1 : 8	No illness	
B. D.	1 : 8	1 : 8	No illness	
S. G.	1 : 8	1 : 8	No illness	
E. H.	1 : 8	1 : 16	No illness	
E. G.	1 : 4	1 : 8	No illness	
S. M.	1 : 8	1 : 16	No illness	
	10-5-37	2-17-38		
M. C.	1 : 4	1 : 8	No illness	10-5-37 through 5-15-38
R. R.	0	0	No illness	10-5-37 through 5-15-38
P. D.	1 : 16	0	No illness	10-5-37 through 5-15-38
L. W.	1 : 4	1 : 2	No illness	10-5-37 through 5-15-38
J. B.	0	0	No illness	10-5-37 through 5-15-38
J. V.	1 : 2	1 : 8	No illness	10-5-37 through 5-15-38
M. C.	1 : 2	1 : 2	No illness	10-5-37 through 5-15-38
J. B.	0	1 : 4	No illness	10-5-37 through 5-15-38
C. C.	1 : 4	1 : 8	No illness	10-5-37 through 5-15-38
E. K.	1 : 4	1 : 8	No illness	10-5-37 through 5-15-38
G. B.	1 : 4	1 : 8	1- 3-38	common cold
G. B.	1 : 8	1 : 8	1-11-38	U. R. I. 99°
M. G.	1 : 2	1 : 4	2- 7-38	common cold
D. C.	1 : 4	1 : 4	3-10-38	common cold
H. C.	1 : 8	1 : 8	2-11-38	otitis media 102.4°
L. M.	1 : 2	1 : 8	3-14-38	U. R. I. 103.4°
V. D.	0	0	2-23-38	common cold
H. V.	1 : 4	1 : 8	12- 7-38	U. R. I. 102°
E. P.	1 : 4	1 : 8	1-17-38	common cold

TABLE 7.—SKILLMAN COLONY—NON-VACCINATED GROUP.

Name.	Complement-fixation test on blood samples collected. 9-23-37 Complete fixation in serum dilution.	2-15-38 Complete fixation in serum dilution.	Clinical history.
D. P.	1 : 16	1 : 16	No illness
M. D.	1 : 8	1 : 8	No illness
E. L.	1 : 32	1 : 32	No illness
R. S.	1 : 8	1 : 8	No illness
M. H.	1 : 8	1 : 4	No illness
A. S.	0	1 : 2	No illness
M. T.	0	0	No illness
F. S.	1 : 8	1 : 8	No illness
M. W.	1 : 8	1 : 8	No illness
M. M.	1 : 16	1 : 8	No illness
S. S.	1 : 16	1 : 16	No illness
G. S.	1 : 4	1 : 2	No illness
I. V.	1 : 16	1 : 16	No illness
I. M.	0	0	No illness
D. R.	0	1 : 2	No illness
B. M.	1 : 8	1 : 4	No illness
H. W.	0	0	Common cold
J. J.	1 : 2	0	Common cold
J. W.	0	0	Common cold
D. W.	1 : 16	1 : 16	Common cold
A. W.	1 : 4	1 : 8	1-15-38 bronchopneumonia
C. W.	1 : 4	1 : 4	Common cold
R. P.	1 : 4	1 : 4	No illness
E. H.	0	0	No illness
A. P.	1 : 2	1 : 4	No illness
D. S.	1 : 2	0	No illness

nated and non-vaccinated during the winter of 1937–38. In each group the sera were taken at the same time, and in all determinations there was little significant change in titer. This lack of change in titer is similar to that shown in Table 2 when the sera were obtained during and following a mild epidemic of respiratory infections, non-influenzal in nature.

Discussion. In these studies constantly low titers of complement-fixing antibodies were found in the same individual over a long period of time if no infection with influenza virus had occurred and even though they had suffered from other types of respiratory infection. Such low titers persisted among hospital personnel in a large urban center as well as in the more isolated State Colonies studied. The general constancy of the titer recorded even in the sera of these individuals studied for more than two years tended to confirm the value of the method.

Repeated vaccination with chick embryo tissue culture vaccine as prepared in large batches for injection[5] did not affect the complement-fixing antibodies, probably for the reason mentioned by Fairbrother.[3b] If the complement-fixing antigen is a soluble substance liberated during multiplication of the virus in the tissues it is also possible that the use of infected mouse lung rather than chick embryo tissue culture vaccine might result in an increase in the complement-fixing antibodies. The effect of such vaccine has not been studied since mouse lung vaccine produces antibodies to the lung protein. However, vaccine derived from chick embryo tissue cultures following parenteral injection produced characteristic increases in the neutralizing properties of sera.* By the same route it also produced in mice immunity to the virus injected, as well as cross-immunity to other strains of human influenza virus.

In a few instances marked elevation in titer of complement-fixing antibodies studied in the sera of individuals following hospitalization established the cause of their respiratory infections as epidemic influenza. Such increases were absent following other types of respiratory infection. By such studies future epidemics of respiratory disease may be more satisfactorily classified as to etiology.

Summary. 1. A study over a 2-year period of complement-fixing antibodies in the sera of individuals vaccinated with chick embryo tissue cultures of active human influenza virus and in the sera of a similar group of non-vaccinated individuals is recorded.

2. In discussion of the complement-fixation test, the titration of the antigen against a known positive serum and the employment of a constant number of antigenic units is suggested.

* Further comparisons are now being made of the complement-fixing antibody titers and the neutralizing antibody titers on the same sera, both before and after vaccination of human beings with chick embryo tissue culture vaccine.

3. The value of repeated complement-fixation tests during and following acute respiratory infections for the diagnosis of epidemic influenza is again emphasized.

We are indebted to the Department of Institutions and Agencies of the State of New Jersey for their interest and coöperation in these studies.

REFERENCES.

(1.) **Fairbrother, R. W.**, and **Hoyle, L.**: J. Path. and Bact., **44**, 213, 1937. (2.) **Francis, T., Jr., Magill, T. P., Rickard, E. R.**, and **Beck, M. D.**: Am. J. Hyg., **27**, 1141, 1937. (3.) **Hoyle, L.**, and **Fairbrother, R. W.**: (*a*) Brit. Med. J., **1**, 655, 1937; (*b*) J. Hyg., **37**, 512, 1937. (4.) **Smith, W.**: Lancet, **2**, 1256, 1936. (5.) **Stokes, J., Jr., McGuinness, A. C., Langner, P. H., Jr.**, and **Shaw, D. R.**: Am. J. Med. Sci., **194**, 757, 1937.

BOOK REVIEWS AND NOTICES.

ENDOCRINE THERAPY IN GENERAL PRACTICE. By ELMER L. SEVRINGHAUS, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin, etc. Pp. 192; 39 illustrations. Chicago: The Year Book Publishers, Inc., 1938. Price, $2.75.

THE author has attempted a concise abbreviation of the current knowledge of endocrinology. It is not surprising, then, to find statements which might be questioned. What is surprising is the author's success in presenting the most sound and clear rationale of endocrine therapy which the Reviewer has seen. The recommendation of diets relatively low in carbohydrate and high in fat for diabetics is not the common practice today. (The author may suffer from them more than the patients.) For the practitioner seeking light in the fog of modern endocrinology this book is strongly recommended. F. L.

A SYMPOSIUM ON CANCER. Addresses by LEIV KREYBERG, CLARENCE C. LITTLE, MADGE T. MACKLIN, EDGAR ALLEN, HOWARD B. ANDERVONT, JAMES EWING, GIOACCHINO FAILLA, HENRI COUTARD, WARREN H. LEWIS, STANLEY P. REIMANN, JAMES B. MURPHY, and EMIL NOVAK. Given at an Institute on Cancer Conducted by the Medical School of the University of Wisconsin. Pp. 202; illustrated. Madison: The University of Wisconsin Press, 1938. Price, $3.00.

THESE 17 papers by 12 well known authors on various aspects of the cancer problem cover a wide range: from genetic and external factors of causation, through various methods of study of the cancer cell—both in the exploration of its nature and in the diagnosis of individual cases—to clinical diagnosis and treatment (one paper each) and the relation of cancer to public health. The contributors, all of whom have done notable work in the laboratories or clinics of this country and Europe, have wisely chosen to expose phases of the problem in which they are especially interested and experienced, rather than to attempt a survey of the whole cancer problem. Details of the individual communications can hardly be considered here; but we can state without reserve that, impossible though it may be to cover the entire subject in such a symposium, yet these papers constitute the best collective statement of very recent progress in cancer research that we have been privileged to read. E. K.

THE ETIOLOGY OF TRACHOMA. By LOUIS A. JULIANELLE, Chairman of the Trachoma Commission, Washington University, St. Louis. Pp. 248; 10 plates (3 in color). New York: The Commonwealth Fund, 1938. Price, $3.25.

THE voluminous literature on the etiology of trachoma makes this book a very welcome edition to everyone interested in the subject. It is not a textbook on trachoma, and does not give any consideration to the treatment of this disease. It is a thorough compilation of all of the experimental work done on the cause of trachoma, including the author's own brilliant researches, and contains a complete bibliography.

F. A.

FRACTURES OF THE JAWS. By ROBERT H. IVY, M.D., D.D.S., F.A.C.S., Professor of Maxillo-Facial Surgery, School of Medicine and Graduate School of Medicine, and of Clinical Maxillo-Facial Surgery, School of Dentistry, University of Pennsylvania, etc., and LAWRENCE CURTIS, A.B., M.D., D.D.S., F.A.C.S., Assistant Professor of Maxillo-Facial Surgery, Graduate School of Medicine, and School of Dentistry, University of Pennsylvania, etc. Pp. 192; 199 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $4.50.

IT gives me great pleasure to express commendation of this work. As stated in the Preface, it represents the knowledge acquired from many years of experience by the co-authors in several large hospitals. Both authors are oral surgeons as well as graduates in dentistry—a happy combination for a patient with a broken jaw. Chapters on anatomy of the facial regions, the complications of fractures here, roentgenograph and the dietary management of such cases are valuable supplements. An especially good feature of the treatment of fractures of these bones is the simplicity of the armamentarium, as compared to the many complex and expensive splints now on the market. This compact, practical treatise is a real addition, valuable alike to student and teacher. E. E.

JACOB HENLE: ON MIASMATA AND CONTAGIA. Translated by GEORGE ROSEN, M.D. Pp. 77; 1 illustration. Baltimore: The Johns Hopkins Press, 1938. Price, $1.00.

THIS translation, reprinted from the Bulletin of the Institute of the History of Medicine, is an extremely important paper, written by one of the most influential 19th century Germans in medicine. Today Henle is too much known through the loops in the kidney that bear his name and too little for the important service that he performed in establishing and applying to human anatomy the newly discovered cell doctrine and preparing the way for a correct knowledge of the nature of infection—the subject of this discourse. This short article is not only a valuable milestone in the history of the theory of infection but also affords an interesting study of logical reasoning that produced important results without presenting any new discovery. It is a welcome addition to a library of medical history. E. K.

EXPERIENCE IN THE MANAGEMENT OF FRACTURES AND DISLOCATIONS (Based on an Analysis of 4390 Cases). By the Staff of the Fracture Service, Massachusetts General Hospital, Boston. Under the General Editorship of PHILIP D. WILSON, M.D., Surgeon-in-Chief, Hospital for Ruptured and Crippled, New York; Clinical Professor of Orthopedic Surgery, College of Physicians and Surgeons, Columbia University, etc. Twenty-three Contributors. Pp. 1036; 1419 illustrations (of which 1192 are line tracings of Roentgenograms in Case Reports). Philadelphia: J. B. Lippincott Company, 1938. Price, $15.00.

THIS book is unique throughout. The authors have recognized that there are many excellent treatises on the principles and practice of the treatment of fractures and dislocations; but they have endeavored to go, and I think very satisfactorily have gone, one step further and have applied specific and individual types of treatment to every kind of fracture met by them in their hospital service. Their data are based on experience with 4390 fractures and dislocations, treated and followed throughout until discharged. The writers very properly regard this extensive contribution as a compilation and collection of material which can be used for further study in arriving at even further conclusions helpful for future patients.

Especially valuable are the excellent follow-up reports of the final results, emphasizing the facts concerned with the poor results, let the blame fall where it may. A numerical scale of rating helps a great deal in visualizing the patients' results.

As the Preface honestly states there are faults of space, allotments, disagreements of minor importance in statistics and other minor criticisms that are insurmountable where there are several authors. The illustrations are many, and in most cases well chosen and clearly descriptive. The serial tracings are especially helpful. It is difficult to limit a work of this sort to a simple report. The technique of open or operative treatment should, I think, be excluded entirely. The indications for and the results of the same are germane.

An honest and successful effort has been made to give readers interested in fractures a valuable and comprehensive reference book based upon careful, thorough and extensive study of a sufficiently large number of cases from which to draw useful conclusions.

E. E.

A Diabetic Primer for Children. By Alfred E. Fischer, M.D., Adjunct Pediatrician and Chief of the Children's Diabetic Clinic, Mount Sinai Hospital, New York City, etc. Pp. 53 (multigraphed). Second edition. Privately published. Obtainable from Dr. Alfred E. Fischer, 73 East 90th Street, New York City. Price, 75 cents.

This booklet should prove useful in the care of children with diabetes. The material is based entirely on accepted theories and plans of treatment and can be placed in the hands of the patient without hesitation. The first part of the booklet is devoted to telling the child the nature of his defect and what it will lead to if he does not take care of himself. This is followed by information about diet, insulin and general care. In a few instances the wording seems as though it would be a little difficult for a child to understand, but on the whole the language is simple.

R. R.

Outline of Roentgen Diagnosis. An Orientation in the Basic Principles of Diagnosis by the Roentgen Method. By Leo G. Rigler, B.S., M.B., M.D., Professor of Radiology, University of Minnesota, Minneapolis. Atlas Edition. Pp. 212; 254 illustrations shown in 227 figures presented in drawings and reproductions of Roentgenograms (Figs. 6 to 51 and 55 to 72 are drawings in an original technic by Jean E. Hirsch). Also Exclusive Text Edition from which the Atlas of Roentgenology has been omitted but to which all figure references have been retained in the text. Philadelphia: J. B. Lippincott Company, 1938. Price, Atlas Edition, $6.50; Student's Edition, $3.00.

This text is a comprehensive outline of Roentgen diagnosis which is admirably suited for teaching. Based upon a series of lectures developed by the author for undergraduate teaching, it presents a very extensive subject in synopsis form.

The book is divided into 11 "sections," each devoted to one portion of the body; for example, thorax, digestive tract, skull, and so forth. The material is handled in outline form. The basic and essential diagnostic criteria are tabulated in numerical order, little attention being given the atypical roentgen manifestations of the more common diseases. Rare and unusual conditions have not been included.

By publishing this work in two forms the author and publishers have considered the question of expense. The student's edition contains no

illustrations; the atlas edition is better bound and includes 227 illustrations arranged in atlas form. The illustrations appear as positive reproductions of original roentgenograms. Their detail is excellent and their legends satisfactory.

Not intended for reference purposes, the books will find their greatest application in undergraduate and graduate teaching. P. H.

THE HORSE AND BUGGY DOCTOR. By ARTHUR E. HERTZLER, M.D. Pp. 322; illustrated. New York: Harper & Brothers, 1938. Price, $2.75.

THIS book has been one of the "best sellers" for months, and, from several points of view, deservedly so. E. K.

HANDBOOK OF HISTOLOGICAL AND CYTOLOGICAL TECHNIQUE. By R. R. BENSLEY, and S. H. BENSLEY, Department of Anatomy, The University of Chicago. Pp. 165. Chicago: The University of Chicago Press, 1938. Price, $2.00.

THIS book is a combination of routine cytological and histological methods for the beginner, and special methods. The latter appear to be a worthwhile collection; the former are not up to date in a number of cases and cannot be enthusiastically recommended for beginners. The dogmatic style in giving instructions seems excusable, in such a handbook. The book is loose-leaf, and perhaps it will be improved in the future by the issuance of revised leaves. If not, there seems to be no justification for this binding. N. S.

ALICE IN VIRUSLAND. By PAUL F. CLARK, Professor of Bacteriology, University of Wisconsin Medical School. Pp. 23; 5 illustrations. Madison, Wis.: Society of American Bacteriologists, 1938. Price, $1.00.

THIS latest parody in the regular Alice tradition is excellent fooling for the medico, which is more than can be said of most 20th century Alices. To be pitied, indeed, is the reader who is "not amused," and few are there who will not be exposed to considerable sound wisdom in the reading process. E. K.

ZUM KREBSPROBLEM UND VERWANDTEN GEBIETEN. Infektion, Regeneration, Zellmutation, Befruchtung. By DR. FRITZ NIEDERMAYER, Chefarzt und Leiter der Chirurgischen Abteilung des Krankenhauses Passau. Pp. 166. Wien: Franz Deuticke, 1938. Price, Paper, M. 5.00; Bound, M. 7.00.

THE author of this booklet appears to be a busy surgeon who two years ago published a monograph on "The Cancer Problem. Thoughts of a Practitioner." In his present paper he defends his previous hypotheses against his numerous critics who are mentioned by name, restating and elaborating his views. Reducing his theory to essentials, he believes that the cancer cell is the result of copulation, or fusion, through previous phagocytosis, of two heterogeneous somatic cells, of which one is an epithelial or connective tissue cell, the other a cell of the reticulo-endothelial system! This is by no means the most fantastic speculation in this very very uncritical composition, which on almost every page discloses the author's lack of training in the fundamental sciences. The last chapter deals with the therapeutic management of cancer and is quite in keeping with the rest.

B. L.

X-RAYS AND RADIUM IN THE TREATMENT OF DISEASES OF THE SKIN. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Director of Department of Dermatology (Skin and Cancer Unit), New York Post-Graduate Medical School and Hospital, Columbia University; Consulting Dermatologist, St. Luke's Hospital, etc. Pp. 830; 308 illustrations, 31 charts and 2 colored plates. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

THERE can be nothing but praise for the third edition of Dr. MacKee's book. Actually it is a new book which has been raised to almost encyclopedic proportions through the energy and ability of no less than 9 collaborators. Each is an expert in his line, whereby authoritative treatment has been secured for all phases of the treatment of dermatoses by Roentgen rays and radium as well as the principles underlying treatment. For example, the physics of Roentgen rays occupies no less than 15% of the entire book. Technique accounts for another 15%. To the biological effects of Roentgen and radium rays, 5% is devoted, and another 5% to histopathology. Altogether, about half of the book is thus devoted to the consideration of the basic science aspects of this specialty within a specialty, a phase that has been long awaiting systematic and authoritative treatment.

The remaining half of the book deals with the particularities in treatment of the various dermatological entities. The closing chapter, on the medicolegal aspects is contributed by a member of the bar and must be of inestimable value to any physician who uses Roentgen rays and radium. Each chapter is concluded by an extensive bibliography.

Photographs of cutaneous lesions are abundant and uniformly excellent, and are selected to the point. The same is true of the photomicrographs and colored plate in the section on histopathology. Graphs and diagrams have not been spared for clarifying the section on the physics of Roentgen rays and radium.

The book is clearly printed on enameled stock. Bold type headings of paragraphs lends to easy reference. In short, no pains have been spared by authors or publisher to make the book comprehensive, attractive, authoritative and sufficient. It is difficult to discover how it could be improved, the volume is in a class by itself in the very forefront of works of its sort.

F. W.

VITAMIN B_1 (THIAMIN) AND ITS USE IN MEDICINE. By ROBERT R. WILLIAMS, Sc.D., of the Bell Telephone Laboratories, New York City, and TOM D. SPIES, M.D., Associate Professor of Medicine, University of Cincinnati. Pp. 411. New York: The Macmillan Company, 1938. Price $5.00.

THIS volume, essentially a review of the extensive literature dealing with the subject of vitamin B_1, is an attempt to bring some sort of order out of chaos. The question might be raised whether the time is yet ripe for such an attempt since the conditions of investigation in many aspects of this field are still so far from uniform as to make evaluation of much of the work almost impossible. For any review of the subject, therefore, to be helpful to the average reader, a very careful critical judgment must be applied to the selection and interpretation of the papers quoted. Such judgment has been exercised with greater success in the second half of this volume (which deals with the historical and experimental aspects of the subject) than is evident in the handling of the first section on vitamin B_1 in the practice of medicine. In this latter section there is also lack of emphasis in presentation of a tremendous amount of detail so that the reader will find it difficult to obtain any clear notion of what constitutes established fact concerning the clinical aspects of vitamin B_1 deficiency. The authors have, however, referred to a vast literature and for this reason the volume will prove a

valuable reference book to those familiar with the field. It will prove of considerably less value to the medical man in search of help in the application of available information to practical problems, and for whom, apparently, the book was in part designed. K. E.

THE PRINCIPLES AND PRACTICE OF PERIMETRY. By LUTHER C. PETER, A.M., M.D., Sc.D., LL.D., F.A.C.S., Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania; Ophthalmologist to the Graduate Hospital of the University of Pennsylvania, etc. Pp. 331; 222 illustrations and 5 colored plates. Fourth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $4.50.

THE fourth edition of this well-known text on perimetry is comparable to the earlier editions in scope and usefulness. As in these, some confusion may occur because of the author's preference for recording fields in the "anatomic fashion." The recent literature on the anatomy of the visual pathways has not been sufficiently covered and most of the literature cited dates prior to 1930. F. A.

THE PHYSIOLOGY OF ANESTHESIA. By HENRY K. BEECHER, A.B., A.M., M.D., Instructor in Anesthesia, the Harvard Medical School; Anesthetist-in-Chief, the Massachusetts General Hospital. Pp. 388. New York: Oxford University Press, 1938. Price, $3.75.

THIS very interesting monograph is based upon material presented in a course on the fundamentals of anesthesia at the Harvard Medical School. The author has succeeded well in describing "the response of the body to anesthetic agents and to anesthesia." Essentially this volume is a presentation of the physiology of anesthesia rather than a textbook of the practice of anesthesia. There are four main chapters, an excellent bibliography and a good working index. The theories of anesthesia are briefly discussed. Local and spinal anesthesia are reviewed from the standpoint of special effects. In the main the volume concerns itself with respiration and circulation during anesthesia, and with the organic effects of anesthetic agents. The Reviewer knows of no volume which covers quite the same ground as does this one or which does the job so well. It will immediately take its place among the valued monographs on anesthesia. I. R.

WORKBOOK IN ELEMENTARY DIAGNOSIS. For Teaching Clinical History, History Recording and Physical Diagnosis. By LOGAN CLENDENING, Professor of Clinical Medicine, University of Kansas. Pp. 167; illustrated. St. Louis: The C. V. Mosby Company, 1938. Price, $1.50.

THIS book is the attempt to carry over into clinical teaching the laboratory notebook method that has so well established its usefulness in the teaching of the fundamental sciences. There is given sufficient in the way of information and outline to serve as a guide for the fledgling clinician without, however, supplanting a more formal textbook. Yet brief though the presentation be, the author has nevertheless in most instances given the explanation of physical signs in the words originally used by those who first described them. Particularly to be commended is the well rounded covering of the subject, instead of the all too frequent overemphasis of examination of heart and lungs. Open to objection is the dismissal of auscultation of the abdomen with the single sentence: "Like children, the abdomen should be seen and not heard." What about fetal heart sounds? Perisplenic or

perihepatic frictions? Altered peristaltic sound? The book is warmly recommended to teachers of physical diagnosis (which the author aptly renames elementary diagnosis) for their consideration and use. R. K.

CANCER. With Special Reference to Cancer of the Breast. By R. J. BEHAN, M.D., DR. MED. (Berlin), F.A.C.S., Cofounder and Formerly Director of the Cancer Department of the Pittsburgh Skin and Cancer Foundation, Pittsburgh, Pa. Pp. 844; 168 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, $10.00.

THIS book was written for the clinician who wishes to enlarge his knowledge of the cancer problem. It is written for "the practitioner . . . whose practice is limited and whose collateral reading is not sufficiently extensive to familiarize him with the more important advances of cancer research and cancer treatment." Although originally begun as a treatise on "Cancer of the Breast" it has been enlarged so that in 29 chapters every phase of cancer has been reviewed. Much of the material reviewed in this volume is irrelevant and poorly chosen. As an example of this the author quotes Sugiura and Benedict as stating that organotherapy has no influence on the growth of cancer cells and one would suppose that he agreed with this statement. Nevertheless, he proceeds to discuss the effect of a wide variety of glandular extracts on cancer tissue.

The chapters on Cancer of the Breast are on the whole very well done and had the volume been limited to this subject it would have received only favorable comment from the Reviewer. As it is, it is a vade medium of cancer of the breast with additional chapters on biophysics and biochemistry, constitutional treatment and radiation. For those who wish a review which in large part is not critically done in the field of cancer research this volume will be useful. The contributions to this field are being made with such rapidity that one wonders whether a volume of this extent is worth while, for it is soon outdated. I. R.

NEW BOOKS.

Pediatric Symptomatology and Differential Diagnosis. By SANFORD BLUM, A. B., M.S., M.D., Head of Department of Pediatrics and Director of the Research Laboratory, San Francisco Polyclinic and Post-Graduate School. Pp. 500; 29 illustrations, including 1 colored plate. Philadelphia: F. A. Davis Company, 1938. Price, $5.00.

Silicosis and Asbestosis. By Various Authors. Edited by A. J. LANZA, M.D., Assistant Medical Director, Metropolitan Life Insurance Company; Chairman, Industrial Hygiene Committee of the New York Tuberculosis and Health Association. Pp. 439; illustrated. New York: Oxford University Press, 1938. Price, $4.25.

Diseases of the Ear, Nose and Throat. By FRANCIS L. LEDERER, B.Sc., M.D., F.A.C.S., Professor and Head of Department of Laryngology, Rhinology and Otology, University of Illinois College of Medicine, Chicago; Chief of the Otolaryngological Service, Research and Educational Hospital. Pp. 835; 457 illustrations and 16 colored plates. Philadelphia: F. A. Davis Company, 1938. Price, $10.00.

The Functions of Human Voluntary Muscles. By NORMAN D. ROYLE, M.D., CH.M., F.R.A.C.S., Honorary Demonstrator of Anatomy, University of Sydney; Senior Orthopædic Surgeon, Lewisham Hospital, Sydney, etc. Pp. 42; 11 illustrations. Sydney: Angus & Robertson, Ltd., 1938. Price, 3/6.

Shock and Related Capillary Phenomena. By VIRGIL H. MOON, A.B., M.Sc., M.D., Professor of Pathology, Jefferson Medical College; Director of Laboratories, Jefferson College Hospital, etc. Pp. 442; 30 illustrations and 5 charts. New York: Oxford University Press, 1938. Price, $3.50.

Die elektrischen Gruppen in Biologie und Medizin (with an English Summary). By RUDOLF KELLER. Pp. 92; 9 illustrations. Zürich: Sperber-Verlag, n.d. (Price not given.)

Subacute and Chronic Pericardial and Myocardial Lesions Due to Non-penetrating Traumatic Injuries. A Clinical Study. By ERIK WARBURG, M.D. With a short Biography of Oluff Borch (Olaus Borrichius) by TORBEN GEILL, M.D. Pp. 147; 18 illustrations. Copenhagen: Levin & Munksgaard, 1938. Price, Kr. 14.00. (London: Humphrey Milford; Oxford University Press. Price, 12s. 6d.)

The March of Medicine. Selected Addresses and Articles on Medical Topics, 1913–1937. By RAY LYMAN WILBUR, M.D., President of Stanford University. Pp. 280. Stanford University, Calif.: Stanford University Press, 1938. Price, $2.75.

The New International Clinics, Vol. IV, N.S. 1 (Old 48th), 1938. Original Contributions: Clinics; and Evaluated Reviews of Current Advances in the Medical Arts. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, with 18 Collaborators. Pp. 349; many illustrations, 1 in color. Philadelphia: J. B. Lippincott Company, 1938.

The Nervous System. A Guide for Use With the Educational Sound Picture "The Nervous System." Prepared by JAMES A. BRILL, Director of Production, Erpi Classroom Films, Inc. In Collaboration with FREDERICK T. HOWARD, Advanced School of Education, Teachers' College, Columbia University, and RALPH W. GERARD, The University of Chicago. Pp. 30; 6 illustrations. Chicago: The University of Chicago Press, 1938. Price, 15c.

Drug Addicts are Human Beings. The Story of our Billion-Dollar Drug Racket. How we Created it and How we can Wipe it Out. By HENRY SMITH WILLIAMS, M.D., B.Sc., LL.D. With a Statement of the Narcotics Problems. By HON. JOHN M. COFFEE, of Washington (Reprinted from the *Congressional Record*). Pp. 273; illustrated. Washington, D. C.: Shaw Publishing Company, 1938. Price, $2.50.

Alice in Virusland. By PAUL F. CLARK, Professor of Bacteriology, University of Wisconsin Medical School. Pp. 23; 5 illustrations. Madison, Wis.: Society of American Bacteriologists, 1938. Price, $1.00. (Review, p. 264.)

Modern Surgical Technic. In 3 Volumes. By MAX THOREK, M.D., K.L.H. (FRANCE), K.C. (ITALY), Professor of Clinical Surgery, Cook County Graduate School of Medicine; Attending Surgeon, Cook County Hospital; Surgeon-in-Chief, The American Hospital, etc. With a Foreword by DONALD C. BALFOUR, M.B., M.D. (TOR.), LL.D., F.A.C.S., F.R.A.C.S., Head of Section in Division of Surgery, The Mayo Clinic; Director and Professor of Surgery, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, etc. Vol. 1, General Operative Considerations, Surgery of the Head and Neck, and Plastic Surgery; Vol. 2, Surgery of the Nerves, Vessels, Bone, Breast and Chest; Vol. 3, Abdominal Surgery, Hernia, Genito-urinary and Gynecologic Surgery. Pp. 2045; 2174 illustrations, originals principally by W. C. Shepard. Philadelphia: J. B. Lippincott Company, 1938. Price, $33.00 per set.

Avian Tuberculosis Infections. By WILLIAM H. FELDMAN, D.V.M., M.S., Associate in Division of Experimental Medicine, Institute of Experimental Medicine; Associate Professor of Comparative Pathology, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 483; 109 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, $7.00.

The British Encyclopædia of Medical Practice. Including Medicine, Surgery, Obstetrics, Gynecology, and Other Special Subjects. Vol. IX. Mumps to Pneumothorax, Spontaneous. Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., SIR LEONARD ROGERS, K.C., S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 805; 117 illustrations and 10 plates (1 in color). London: Butterworth & Co. (Publishers), Ltd., 1938. Price, $12.00.

Mental Disorders in Urban Areas. An Ecological Study of Schizophrenia and Other Psychoses. By ROBERT E. L. FARIS, and H. WARREN DUNHAM. Pp. 270; 37 maps, 96 tables and 2 charts. Chicago: The University of Chicago Press, 1939. Price, $2.50.

Scarlet Fever. By GEORGE F. DICK, M.D., D.Sc., Professor of Medicine, University of Chicago; Attending Physician, Billings Memorial Hospital, etc., and GLADYS HENRY DICK, M.D., D.Sc. Pp. 149; 8 colored plates and 4 charts. Chicago: The Year Book Publishers, Inc., 1938. Price, $2.00.

The Wheel of Health. A Study of a Very Healthy People. By G. T. WRENCH, M.D. (LOND.). Pp. 146; 1 illustration. London: The C. W. Daniel Company, Ltd., n.d. Price, 6/–.

NEW EDITIONS.

Allergic Diseases. Their Diagnosis and Treatment. By RAY M. BALYEAT, M.A., M.D., F.A.C.P., Associate Professor of Medicine and Lecturer on Diseases Due to Allergy, University of Oklahoma Medical School; Chief of the Allergy Clinic, University Hospital, etc. Assisted by RALPH BOWEN, B.A., M.D., F.A.A.P., Chief of Pediatric Section, Balyeat Hay Fever and Asthma Clinic, Oklahoma City, Okla. Pp. 547; 145 illustrations, including 8 in colors. Fifth edition, revised and enlarged. Philadelphia: F. A. Davis Company, 1938. Price, $6.00.

Urology. By DANIEL N. EISENDRATH, M.D., Consulting Urologist to the American Hospital, Paris, France; formerly Attending Urologist, Michael Reese and Cook County Hospitals, etc.; and HARRY C. ROLNICK, M.D., Attending Urologist, Michael Reese, Mt. Sinai, and Cook County Hospitals, Chicago, etc. Pp. 1061; 750 black and white illustrations and 12 in color. Fourth edition, entirely revised and reset. Philadelphia: J. B. Lippincott Company, 1938. Price, $10.00.

Classic Descriptions of Disease. With Biographical Sketches of the Authors. By RALPH H. MAJOR, M.D., Professor of Medicine, University of Kansas School of Medicine. Pp. 727; illustrated. Second Edition. Springfield, Ill.: Charles C Thomas, 1930. Price, $5.50.

PROGRESS
OF
MEDICAL SCIENCE

OPHTHALMOLOGY.

UNDER THE CHARGE OF
WILLIAM L. BENEDICT, M.D.
HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,
AND
H. P. WAGENER, M.D.
ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

OPTOCHIASMATIC ARACHNOIDITIS.

In the last 10 years, increasing attention has been paid to the ocular syndromes caused by local arachnoiditis in the region of the chiasm and intracranial portion of the optic nerves, and especially to their diagnosis and surgical treatment. No single type or mode of loss of vision has been found to be pathognomonic of this lesion. Published case reports include practically every possible form of acute and chronic involvement of the chiasm or of the optic nerves anterior to the chiasm. No definite etiology has been assigned to the condition. It seems quite possible that some cases of acute retrobulbar neuritis have been subjected to intracranial surgery under the probably mistaken diagnosis of chiasmal or prechiasmal arachnoiditis. Some neurosurgeons are inclined to doubt either the existence of this lesion as a primary clinical entity or the efficacy of surgical intervention. Yet there seems to be rather conclusive evidence that certain hitherto hopeless cases of progressive optic atrophy can be benefited by the removal of obvious constricting fibrous bands around the nerves, even though the exact underlying etiology and pathology of these bands is not known. And it seems possible that ultimately a clear-cut syndrome may evolve which will enable the ophthalmologist to further reduce the number of optic atrophies which he must classify at present as of unknown etiology and not amenable to treatment. It would seem that sufficient data has been accumulated now in widely separated centers to warrant a review of our present knowledge of the subject.

According to Vail,[13] the entity of chronic arachnoiditis was established in its generalized form by Quincke in 1893 and in its localized form by Schlesinger in 1898. In February, 1929, Cushing and Eisenhardt[5] stated that, in a few cases explored because of a suspected suprasellar neoplasm, nothing was found but a local collection of slightly xanthochromic fluid, the evacuation of which led to a subsidence of symptoms. In such cases the presumptive diagnosis of chronic cisternal arachnoiditis was made, though Cushing seemed unwilling to regard such a diagnosis as proved in the absence of necropsy.

Apparently the first report confined to optochiasmatic arachnoiditis as a clinical surgical entity was that published by Balado[1] in 1929. In his case, progressive loss of vision for 6 months, pallor of disks with slight loss of substance, and a bitemporal type of defect in the fields of

vision led to an exploration of the chiasmal region. Localized arachnoiditis was the only lesion found. Histologic examination of a biopsy specimen of the arachnoid revealed a proliferation of the endothelial cells and some small calcareous nodules. The vision improved somewhat after the operation.

In 1930, Deery[7] published the findings in 170 cases operated on in Cushing's Clinic during a 10-year period because of the presence of a chiasmal syndrome. He stated that in 13 cases (7.5%) the only positive finding was a definite thickening of the arachnoid with an abnormally large collection of fluid about the chiasm and optic nerves. Optic atrophy was present in 11 of these cases and choked disks in 2. Bitemporal hemianopsia was noted in 7 cases, homonymous hemianopsia in 2, and scotomas (probably central) in 4. Again there was hesitancy in accepting this lesion as a definite clinical entity. Deery noted that 2 similar patients with thickened arachnoid had proved to have syphilis. Later in the same year, Cushing[4] reported a case with cecocentral scotomas and irregular bitemporal contraction in which exploration revealed demonstrable thickening of the arachnoid constituting the cisterna chiasmaticus with a large accumulation of fluid. The vision failed to improve following evacuation of the fluid. Cushing stated: "The diagnosis of cisternal arachnoiditis, however, is one that I am exceedingly loath to make in the absence of postmortem examination, for one may be easily deluded, and not a few patients with symptoms ascribed to such a process have subsequently proved to have tumor." Also, Cushing was not willing to accept the etiologic relationship of nasal accessory sinus disease to this form of arachnoiditis. In the same year, in discussing the subject of cerebral pseudotumors, Frazier[8] mentioned 5 cases with signs suggesting pituitary lesions and stated that they were improved after operation.

In 1931, Davis and Haven[6] described three types of lesions in the intracranial arachnoid membrane, inflammatory, fibrous and hyperplastic. Included in their series were 2 cases with involvement of the prechiasmal portion of the optic nerves. In both of these cases, the lesion was of the fibrous type. One case, in which the possibility of Leber's hereditary optic atrophy was considered, showed only adhesions around the optic nerves. In the other case, in which vision was reduced to light perception only, an enormously dilated cisterna chiasmaticus was found. In both cases, histologic examination revealed marked thickening of the reticular structure of the arachnoid due to an increase in the fibrous elements with a moderate amount of leukocytic infiltration. Vision improved in both cases after surgery.

It will be noted that some reports emphasize only the adhesions around the chiasm and optic nerves, while others stress the dilatation of and accumulation of fluid in the cisterna chiasmaticus. The difference in these two points of view or two types of lesion is clearly brought out in two reports published in 1931. Heuer and Vail[10] reported 4 cases of "chronic cisternal arachnoiditis" in all of which the cisterna chiasmaticus was markedly distended with fluid. In 1 of the cases, central scotomas with temporal contraction of the peripheral fields were present, in 2 concentric contractions, and in 1 total blindness. At operation, the fluid in the cistern was evacuated, the wall of the cistern was excised, and the chiasm and optic nerves were freed from adhesions. Vision improved in all cases. Craig and Lillie[3] reported 8 cases of

"chronic local arachnoiditis" in all of which the presence of arachnoiditis with adhesions around the chiasm and optic nerves was noted. Bitemporal hemianopsia was present in 4 cases, homonymous hemianopsia with central scotoma in 3, and unilateral nasal hemianopsia in 1. Vision improved after operation in only 2 cases. Three cases came to necropsy. In 1 of these, necropsy revealed chronic basilar arachnoiditis with chronic local arachnoiditis and marked adhesions around the chiasm. In the other 2 cases, necropsy revealed basal meningitis with encephalitis. In 1 case, there was additional gliosis of the aqueduct.

Also in 1931, Vincent, Puech and David[14] reported 7 cases of optochiasmatic arachnoiditis in which adhesions around the nerves were the outstanding findings. Central scotomas were present in 4 cases, concentric contraction in 2, and temporal contraction in 1. In 3 cases the vision was considerably improved after operation; in 3 cases it remained stationary; in 1 the loss of vision progressed in spite of surgery. The authors felt that the characteristic features suggesting the diagnosis of chiasmal arachnoiditis were: 1, rapid loss of vision, at first with normal fundi and later with simple optic atrophy; 2, frequently central scotomas early, bitemporal hemianopsia rare or late; 3, mild evidences of infection and an episodal rather than a steadily progressive loss of vision; 4, normal sella; and, 5, absence of signs of pituitary insufficiency.

Since these early reports, a number of cases (approximately 130) have been cited in the literature. A few points of interest are worthy of especial note. In 1937, Rubino[11] reported 5 cases which he diagnosed as optochiasmatic arachnoiditis. He treated 3 of these medically, with improvement in 1 and no improvement in 2, and 2 surgically with improvement in both. He thought that better results were to be expected from surgery if hydrocephalus of the chiasmal cistern was found and not merely adhesions. In the medical treatment he employed fibrolysin and iodides. He felt that if progressive loss of vision continued under medical treatment, surgery should be instituted.

In 1937, Hausman[9] suggested that syphilitic arachnoiditis in the neighborhood of the chiasm might be the cause of some of the cases of progressive atrophy in syphilitics in whom a definite diagnosis of tabes cannot be established. He reported 4 cases, in each of which there was a typical chiasmal syndrome with primary optic atrophy and heteronymous field defects. Three were treated medically and 1 surgically. In this 1 case adhesions were found around the chiasm and were separated. This was the only case that showed any improvement in vision and fields. He concluded, therefore, that surgical treatment was the method of choice in cases of this type, especially when blindness is imminent. A fifth case showed bilateral papilledema with concentric contraction of the fields without increased intracranial pressure or dilatation of the ventricles. Necropsy on this case revealed diffuse perichiasmal gummatous meningitis with definite syphilitic exudate into the chiasm. Other syphilitic lesions were present in the brain also.

In 1938, Vail reported 4 more cases of "optochiasmic arachnoiditis." In 3, the diagnosis was confirmed at operation. The fourth case was treated with injections of typhoid vaccine intravenously, large doses of sodium salicylate, frequent spinal drainage, and sodium iodide intravenously. Recovery was satisfactory. One of the cases which showed at operation an accumulation of fluid in the chiasmal cistern later developed typical findings of multiple sclerosis. Vision improved only

slightly following surgical intervention. Vail suggested that the characteristic appearance of the optic disks in cases of chiasmal arachnoiditis is that of a mixed atrophy, an atrophy of simple type with narrowing of the retinal vessels or with mild blurring of the disk margins.

In a review of the subject of retrobulbar neuritis, Schieck[12] accepts the views of Burgeois, Puech and their coworkers on the etiology and pathogenesis of optochiasmatic arachnoiditis. They state that the cerebrospinal fluid is contained not in the subarachnoid space but between two layers of arachnoid, one adherent to the dura and the other adherent to the pia. This space between the two layers of the arachnoid widens in some places as in the chiasmal cistern. Adhesions between these two layers may follow even mild inflammations and can result in a ballooning out of the normally wider spaces sufficient to cause pressure on the chiasm and optic nerves. Optochiasmatic arachnoiditis, they state, may arise as a late sequence of trauma such as skull fracture, as a complication of nasal accessory sinus disease, mastoiditis or petrositis, or as a sequel of encephalitis either non-specific or due to lues, of multiple sclerosis or of tuberculosis.

In 1937, Bollack, David and Puech[2] published a very complete review of our knowledge to date on the subject of optochiasmatic arachnoiditis. On the basis of 129 cases, 63 collected from the literature and 66 of their own, these authors summarized the clinical symptoms of optochiasmatic arachnoiditis. The primary symptom is loss of vision, which may occur suddenly or gradually, usually the latter, and which is usually unilateral at first though both eyes may be involved immediately. Central vision may be good but usually is considerably reduced, and blindness may be complete in one or both eyes. Defects in the peripheral fields of vision are the most constant findings. The three most frequent types are: 1, temporal or bitemporal hemianopsia; 2, concentric contraction; 3, central scotomata; less frequent findings are: 4, nasal contraction; 5, homonymous hemianopsia; and, 6, altitudinal contraction.

Bitemporal hemianopsia occurs in only about 17% of the cases of chiasmal arachnoiditis and is usually later in development, more irregular in outline, and more atypical in character than in tumors in the region of the chiasm. It may be accompanied by concentric contraction of the residual fields and by central scotomata. Bitemporal hemianopsia for colors is not an early sign of chiasmal arachnoiditis.

Concentric contraction of the fields of vision occurs in about 23% of the cases. It may be slight or extreme in degree. It is usually irregular in type and may be accompanied by temporal contraction, central scotomata, or homonymous hemianopsia.

Central scotomata are found in about 31% of the cases and are therefore the most frequent finding. They occur usually early in the course of the disease. They are usually bilateral and absolute and usually large. They may be of cecocentral type, directly central, or paracentral. They are associated often with temporal hemianopsia, homonymous hemianopsia, nasal hemianopsia, or concentric contraction.

Nasal contraction is usually an early phase of concentric contraction but it may be more definitely a nasal or binasal hemianopsia. It occurs in about 7% of the cases. It indicates involvement of the prechiasmal portion of the optic nerves rather than of the chiasm. It is often accompanied by central scotomata.

Homonymous hemianopsia occurs in about 5% of the cases and is associated usually with central scotomata or with considerable reduction of central vision. It indicates a rather diffuse lesion with involvement of the optic tracts as well as of the optic nerves.

Altitudinal contraction occurs in about 5% of the cases. It is usually of inferior type but occasionally involves the upper fields. It may be associated with central scotomata.

In 12% of the cases, the fields of vision were either normal, not reported, or could not be obtained because of poor vision.

Ophthalmoscopically, the optic disks are found to be normal in 10% of the cases, show primary optic atrophy involving the whole disk in 38%, temporal segmental pallor in 7%, partial horizontal atrophy in 4%, post-inflammatory optic atrophy in 10%, post-edematous optic atrophy in 6%, simple hyperemia in 7%, choked disks in 10%. In 8% the appearance of the disks is difficult to classify. It must be remembered that the aspect of the disks may be different in the same case at different stages of the disease. The presence of choked disks probably indicates that the arachnoiditis has extended toward the posterior part of the base and has invaded the cisterna magna or else that there is an added ventricular hydrocephalus.

Rather rarely, involvement of the third, fifth or sixth nerves, or nystagmus, occurs in association with the optic nerve lesions of chiasmal arachnoiditis. Headache, usually bifrontal or fronto-temporal, may be an early symptom and may precede the loss of vision. It may be accompanied by somnolence and occasionally by vomiting and vertiginous attacks. Rarely, polydipsia, polyuria and obesity occur, or an atypical adiposo-genital syndrome. Convulsions or mental changes may occur in rare cases. In most instances, however, the symptoms and findings are confined to the eyes and examination of the rest of the nervous system yields negative results. Anosmia, facial paralysis, or affections of the eighth nerve are found occasionally. The spinal fluid is usually normal. At times, a mild increase of cells and protein is found.

Roentgenograms of the sella turcica should be normal in cases of chiasmal arachnoiditis. Exceptionally, enlargement of the tuberculum sellæ, enlargement of the sella with thinning of the posterior clinoids, atrophy of the anterior clinoids and of the small wing of the sphenoid have been reported. But, in the main, the diagnosis has not been verified in these cases. Essentially, the optic foramina are always normal. However, 1 case of proven cystic serous meningitis showed enlargement of both optic foramina and a a deformity of the sella characteristic of glioma of the chiasm. Exceptionally, the roentgenograms reveal some spots of calcification. Roentgenograms of the skull may reveal increased vascularity or spreading of the sutures. Roentgenograms of the sinuses may reveal cloudiness of one or more of the sinuses or perisinusitis. Ventriculograms are normal usually. Occasionally, they show mild internal hydrocephalus. In a few instances the ventricles are seen to be small and most of the air is in the subarachnoid spaces. Exceptionally, air will be seen to have entered a subarachnoid cyst.

In general, the purely ocular symptomatic forms of chiasmal arachnoiditis may be classified into three groups: 1, the syndrome of axial neuritis, acute or chronic (25% of the cases); 2, the syndrome of simple atrophy (13% of the cases); and 3, the chiasmal syndrome (15% of

the cases). In the remaining 47% of the cases, the ocular lesions are more atypical or are associated with signs of involvement of other parts of the brain.

The differential diagnosis of chiasmal arachnoiditis from other lesions affecting the prechiasmal and chiasmal portions of the optic nerves is very difficult to establish positively before operation. The diagnosis may be suggested by the rather atypical course of the disease and its tendency to advance in successive episodes, by the association of evidences of inflammation of neighboring structures, by the etiologic factors of trauma, sinusitis or encephalitis, and by the fact that roentgenograms of the head, ventriculograms and spinal fluid are normal. Cases that develop in the form of acute axial neuritis must be differentiated from multiple sclerosis, in which the lesion is more often unilateral and has a tendency to rapid spontaneous improvement; from neuromyelitis optica, in which characteristically there is rapid development of the signs of a progressive myelitis; from encephalitis, especially if this is atypical in its course or if it is complicated by arachnoiditis, and from the retrobulbar neuritis due to sinusitis, which is especially difficult since sinusitis may be the cause of the arachnoiditis.

Cases that develop in the form of chronic retrobulbar neuritis must be differentiated from toxic amblyopia, in which the course is normally more gradual and uniformly progressive and in which the toxic substance is usually known; from Leber's disease, in which the family history is of the greatest importance, and from tumors in the basofrontal and prechiasmal regions, in which the roentgenographic findings and ventriculogram aid in the diagnosis.

Cases that develop in the form of simple optic atrophy with concentric contraction of the peripheral fields are to be differentiated particularly from atrophies due to syphilis.

Cases that present the typical chiasmal syndrome must be differentiated from the various types of tumors occurring in this region.

Medical treatment may be tried in the early stages of the disease. The remedies suggested are cyanide of mercury, iodides, sodium salicylate, urotropin, neurotropic vaccines, vitamin B_1, and Roentgen ray. If these measures fail to control the progress of the disease, surgical intervention is justified.

On exploration, lesions of three types may be encountered: 1, arachnoiditis; 2, serous meningitis; and, 3, optic atrophy. The term arachnoiditis is applied to the interlacing of arachnoidal fibers which ensheathes the optic nerves and the chiasm and fixes them to the neighboring structures, especially to the large vessels. This is associated often with engorgement of the adjacent veins. The arachnoidal network may be composed of: 1, very fine filaments; 2, solid, well-limited bands which compress the nerves; 3, a sheet of arachnoiditis masking the entire region; 4, calcareous plaques may be added to the plastic formations; 5, arachnoidal adhesive bands with associated vascular bands. Serous meningitis of the chiasmal cistern with arachnoidal cysts also may appear under several forms: 1, a suprachiasmal arachnoid cyst which may simulate a tumor; 2, an intrasellar arachnoid cyst which may give rise to a forward bowing of the sella similar to that seen in glioma of the chiasm; 3, multiple cysts; and, 4, gelatinous tissue. In the cases which are designated as optic atrophies, the nerves are atrophic but no definite arachnoidal adhesions are found. Histologic

examination of the optic nerves in any of these types of arachnoiditis reveals peripheral neuritis with demyelinization and atrophy of a certain number of nerve fibers.

In a series of 254 explorations of the chiasmal region which were analyzed by Bollack, David and Puech, 71 (27%) proved to be chiasmal arachnoiditis. In a series of 95 cases of chiasmal arachnoiditis, the immediate mortality was about 7.5%. Recurrence of the condition occurred in two forms, an immediate, which started within 12 to 15 days following surgery, and a late, which started several months after surgery. Recurrences of each of these types were noted in 3 cases, a total of 6%. Of the cases collected from the literature, 46% showed improvement after operation, and in 20% the operation was a complete failure. Definite improvement was noted in 28% of their own cases. The results were found to be poor usually in cases in which the symptoms were of several years' duration, although improvement was noted even in a few of these. The best results were noted in cases of less than a year's duration. Cases operated on within a few weeks of the onset of loss of vision have good results usually, but in such cases it is not at all certain that improvement in vision would not have occurred under medical treatment. Of the 19 good results obtained by Bollack and his associates, 11 were in cases of less than a year's duration. However, not all cases of less than a year's duration improve. Cases with very poor vision or even complete blindness may improve if the blindness is not of too long standing. Ophthalmoscopically visible atrophy of the optic nerves is not a contraindication to surgery, since some cases improve in the presence of apparently complete atrophy. Edema of the disks or normal disks are usually good prognostic signs. Of the 19 good results noted by Bollack, 5 had normal optic disks. Of 29 improved cases collected from the literature, 9 had shown impairment of central vision without defects in the peripheral fields, 8 had shown defects in the peripheral fields without loss of central vision, and in 12 both central and peripheral vision had been involved. In Bollack's series of 19 improved cases, 10 had shown loss of central vision without peripheral field defects, 3 had shown peripheral field defects only, and in 6 both central and peripheral vision had been affected before operation. The associated symptoms such as headaches, somnolence, epileptiform attacks, mental disturbances, and diabetes insipidus, may improve after operation also.

It is of some interest to note the type of lesion found in the cases in which the results of operation were favorable. Of 25 improved cases collected from the literature in which the data were available, 12 showed arachnoidal adhesions only, 3 purely cystic lesions, and 13 a mixed type of lesion. Among 14 improved cases in the series of Bollack and his coworkers, arachnoidal adhesions only were found in 3, cysts alone in 3, and mixed lesions in 9. It is impossible to tell from the gross appearance of the optic nerves at operation whether improvement in vision will be obtained.

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REFERENCES

(1.) **Balado, M.**, and **Satanowsky, P.**: Arch. Argent. de Neurol., **4**, 71, 1929. (2.) **Bollack, J., David, M.**, and **Puech, P.**: Optochiasmatic Arachnoiditis, Paris, Masson et Cie. 1937. (3.) **Craig, W. McK.**, and **Lillie, W. I.**: Arch. Ophth., **5**, 558.

1931. (4.) **Cushing, H.**: Ibid., **3**, 704, 1930. (5.) **Cushing, H.**, and **Eisenhardt, L.**: Ibid., **1**, 168, 1929. (6.) **Davis, L.**, and **Haven, H. A.**: J. Nerv. and Ment. Dis., **73**, 286, 1931. (7.) **Deery, E. M.**: Ibid., **71**, 383, 1930. (8.) **Frazier, C. H.**: Arch. Neurol. and Psychiat., **24**, 1116, 1930. (9.) **Hausman, L.**: Ibid., **37**, 929, 1937. (10.) **Heuer, G. J.**, and **Vail, D. T., Jr.**: Arch. Ophth., **5**, 334, 1931. (11.) **Rubino, A.**: Riv. otol. ecc., **14**, 552, 1937. (12.) **Schieck, F.**: Zentralbl. f. ges. Ophth., **41**, 193, 1938. (13.) **Vail, D.**: Arch. Ophth., **20**, 384, 1938. (14.) **Vincent, C., Puech, P.**, and **David, M.**: Rev. neurol., **1**, 760, 1931.

PHYSIOLOGY

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The Influence of the Erythrocytes Upon the Oxygenation of the Blood of Fish. E. C. Black, Laurence Irving and R. W. Root (Martin Biological Laboratory, Swarthmore College, and College of the City of New York). The respiratory pigments of vertebrates and invertebrates are in general half saturated with oxygen at pressures lower than 10 mm. Such ease of saturation favors oxygenation, but it means that the unloading of oxygen into the tissues is not provided with a pressure adequate to secure diffusion into the tissues. The introduction of CO_2 into the blood of fishes, however, raises the pressure of oxygen at 50% saturation in proportions of from 1 to 6 mm. for each added millimeter of CO_2. The bloods of 3 fresh-water and 3 marine fishes have been examined. In 5 cases the effect of CO_2 in raising the pressure of oxygen necessary for half saturation is practically abolished by hemolysis; in 1 it is greatly diminished by hemolysis.

The effect of CO_2 has been attributed to its influence as an acid in diminishing the affinity of hemoglobin for oxygen. But inasmuch as CO_2 does not affect the hemoglobin in hemolyzed blood, it appears that it is only the hemoglobin in the corpuscle which is sensitive to the influence of CO_2. The sensitivity must be due primarily to the operation of CO_2 upon the intact corpuscle. While ultimately it is the affinity of hemoglobin for oxygen which makes possible the respiratory transport of oxygen, these specific properties of the blood of fishes are in the first analysis attributable to the behavior of the erythrocytes.

The Carbohydrate of the Gonadotropic Hormone of Pregnancy Urine. S. Gurin, C. Bachman and D. W. Wilson (Laboratories of Physiological Chemistry, and Obstetrics and Gynecology, University of Pennsylvania). A modified process has been developed by which highly active gonadotropic hormone preparations can be obtained from early pregnancy urine. After preliminary adsorption upon benzoic acid by the Katzman-Doisy technique, the crude hormone so obtained is further purified by extraction with 50% alcohol at pH 6, followed by addition of 2 volumes of alcohol to the alcoholic extract. The resulting precipitate is then extracted with 50% alcohol at pH 4.8 and the hormone thrown out of solution by the addition of an equal volume of absolute alcohol. The resulting product has been found active in 0.35–1.0 γ, thus containing 1000–3000 minimal ovulating doses per mg. when assayed by the Friedman technique.

These preparations contain carbohydrate, hexosamine, acetyl and polypeptide groups while pentose, uronic acid and keto-hexose appear to be absent. As has been previously observed by Meyer, the hormone appears to have the chemical and physical properties of a mucoid.

The molecular ratios of reducing sugar to hexosamine suggest the presence of carbohydrate units consisting of 1 hexosamine and 2 hexose groups. By means of the carbazole and orcin reactions it has been established that the non-hexosamine carbohydrate of several of our best preparations is entirely galactose. The ratio of galactose (determined by the carbazole method) to hexosamine is 2 to 1.

The Electromotive Forces Produced by Alkaloids in Oil Batteries. R. BEUTNER (Department of Pharmacology, Hahnemann Medical College). In several publications, some of which date back as much as 27 years, I have demonstrated the electrode-like properties of water-insoluble electrolytic conductors. An oil mixture containing, for example, cresol and an organic acid acts as an electrode which is reversible for various cations, while an oil such as toluidin is reversible for anions. An attempt is now being made to use such oil batteries for analytical purposes.

Just as a hydrogen electrode is used for measuring hydrogen ion concentrations, so also is it possible to measure the concentration of certain other ions in a solution by placing a suitable oil electrode in that solution, for example, alkaloidal concentrations in galenical preparations can thus be estimated.

The "oil" electrode which we used contained a mixture of nitrobenzene with 10% oleic acid; this mixture is filled into a cup which is attached to a calomel electrode. A cup-shaped electrode is immersed into a 0.1% solution of sodium oleate, or sodium benzoate. This solution is directly connected with another electrode and the E.M.F. is measured by means of an electrometer.

The measured system is therefore:

(1)

KCl, sat'd.	Nitrobenzene + 10% Oleic acid	Na Oleate
−	0.1 Volt	+

in which the positive pole is on the side of the sodium salt of the organic acid. To this organic salt solution we added varying small amounts of alkaloidal salts. This addition markedly decreases the E.M.F. of system (1), even in amounts as low as 1 to 1,000,000.

Such a drop in E.M.F. is specific for alkaloids and can be used for their determination.

The action of the alkaloidal salt is due to the fact that it produces the E.M.F. in the opposite direction. A system like:

(2)

KCl, sat'd.	Nitrobenzene + 10% Oleic acid.	Alkaloidal salt
+		−

has its E.M.F. in the opposite direction.

The E.M.F. of such systems as (1) and (2) is due to the potential differences located at the phase boundary of the nitrobenzene and the various watery solutions. The organic salt, sodium oleate, or an alkaloidal salt, penetrates more than an inorganic salt, but the sodium oleate carries positive sodium ions and the alkaloidal salt carries negative sulphate ions into the nitrobenzene. This explains their antagonistic action. The theory is explained in detail in the lecture and graphs are presented which show the observed relation between alkaloidal concentration and drop of the E.M.F. of system (1) after addition of alkaloids.

The powerful electrical action of alkaloids as observed in systems of this type suggests a possible explanation of their action.

We expect to study by a similar technique the concentration of alkaloidal hormones like epinephrine, histamine, acetyl-choline, and their presence in biological fluids.

The Long Persistence of Excitation at a Synapse. M. G. LARRABEE and D. W. BRONK (Johnson Research Foundation and The Institute of Neurology, University of Pennsylvania). The long persistence of an excitatory state in the central nervous system has usually been attributed to the continued arrival of impulses over delayed paths or long chains of neurons. It has been further assumed that each volley of impulses arriving at a cell in the central nervous system or in a sympathetic ganglion produces a discharge of but one impulse.

The present experiments show, however, that an excitatory state can persist for a long time in a synaptic region. The investigations have been made on the stellate ganglion of the cat—a structure in which there are no complex neuronal chains. We find that rapidly repeated preganglionic volleys produce a synaptic effect which lasts for many seconds or even minutes, as a result of which: 1, cells continue to discharge impulses for many seconds after the end of preganglionic stimulation; and, 2, more cells respond to a given preganglionic volley than before the conditioning stimulus. Because impulses entering the cell antidromically reduce rather than increase their responsiveness to preganglionic volleys and do not produce after-discharge, the long-lasting change in the properties of a ganglion is not attributable to previous activity of the ganglion cells themselves but rather to some alteration in the properties of the synaptic mechanism.

The long persistence of this change in properties of the synaptic region, which may be referred to as an excitatory state, requires some modification of the acetylcholine hypothesis for synaptic transmission. If excitation is due to liberation of acetylcholine from the terminations of the presynaptic fibers, it will be necessary to assume that it is not as rapidly destroyed as has been previously assumed. Or, on the other hand, it may be necessary to conclude that there are other accompaniments of presynaptic activity which leave long-lasting effects capable of producing excitation of the postsynaptic cells.

The Irritability Cycle of Nerve Cells for Excitation by Acetylcholine. D. W. BRONK and M. G. LARRABEE (Johnson Research Foundation and The Institute of Neurology, University of Pennsylvania). As a wave of propagated activity passes a given region of a nerve cell, that portion of the cell surface is electrically negative relative to an inactive region. Thereafter it becomes successively positive, negative, and again posi-

tive. Gasser and his associates have shown that the positive phase of these after-potentials is correlated with a state of the nerve in which it is less readily stimulated by an electric current; during the phase of the negative after-potential it is more irritable than before activity. These facts suggest that the after-potentials are useful indicators of the readiness with which nerve cells will respond to stimulation.

In the normal functioning of the central nervous system, however, excitation is generally accomplished by nerve impulses arriving at the synapses. Rosenblueth and Simeone (*Am. J. Physiol.*, **122**, 688, 1938) maintain that this excitation is due to acetylcholine rather than to the action current of the presynaptic impulses and conclude that there is therefore no parallelism between after-potentials and synaptic excitation.

In order to settle this issue we have excited nerve cells in a sympathetic ganglion by continuous perfusion with appropriate concentrations of acetylcholine and have, at the same time, recorded the impulses they discharged into the postganglionic nerve. During such chemical excitation we have produced a further rapid excitation of the cells by repeated volleys of preganglionic and antidromic impulses. Following these periods of activity, we have observed the development of a large ganglionic positive after-potential. During the course of this after-potential, fewer cells were observed to respond. As the potentials decreased there was again a more active discharge of impulses, there being a close parallelism between the degree of inexcitability and the magnitude of the potential.

The positive after-potential is therefore a measure of the inexcitability of nerve cells for either electrical or chemical excitation and is, accordingly, a useful sign of the irritability of ganglia or groups of cells in the central nervous system.

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